S. HRG. 103–50

THE FEDERAL GOVERNMENT'S INVESTMENT IN NEW DRUG RESEARCH AND DEVELOPMENT: ARE WE GETTING OUR MONEY'S WORTH?

HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

WASHINGTON, DC

FEBRUARY 24, 1993

Serial No. 103–1

Printed for the use of the Special Committee on Aging

U.S. GOVERNMENT PRINTING OFFICE

66–959 WASHINGTON : 1993

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-040848-2

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THE FEDERAL GOVERNMENT'S INVESTMENT IN NEW DRUG RESEARCH AND DEVELOPMENT: ARE WE GETTING OUR MONEY'S WORTH?

WEDNESDAY, FEBRUARY 24, 1993

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee met, pursuant to notice, at 9:35 a.m. in room G–50, Dirksen Senate Office Building, Hon. David Pryor (Chairman of the Committee) presiding.

Present: Senators Pryor, Cohen, Grassley, Kohl, Durenberger, Shelby, and Feingold.

Staff present: Portia Porter Mittelman, staff director; Christine Drayton, chief clerk; John Coster, professional staff; Mary Berry Gerwin, minority staff director/chief counsel; and Victoria Blatter, professional staff.

OPENING STATEMENT OF SENATOR DAVID PRYOR, CHAIRMAN

The CHAIRMAN. Good morning, ladies and gentlemen. We welcome all of you this morning to this hearing.

Today we are going to examine the issues surrounding the Federal Government's role in the research and development of new drugs. Each year, the Federal Government, the taxpayer, spends billions of dollars to help find drugs to treat the diseases of our generation: cancer, Alzheimers, high blood pressure, diabetes, AIDS, and other chronic conditions. Yet, there is evidence that the taxpayers who support the development of these drugs are being charged unreasonable prices by those private drug manufacturers, which are given the exclusive license to patent and to sell these drugs.

Our Government is not in the business of manufacturing and distributing drugs. That is precisely the responsibility of the private drug companies. However, the private drug manufacturers today need the Federal Government's support to research and develop these new drugs just as much as the Federal Government needs these companies to bring new drugs to the market.

However, the supposed mutual partnership, I fear, has become a one-way street. In some cases, it appears to have degraded into nothing more than a unilateral agreement, where one side does one thing, and the other does little.

Drug manufacturers appear to have found the key that unlocks the Federal Government's scientific vault, which is teeming with

dozens upon dozens of drugs that have lucrative markets. Stuck holding the bag are American citizens, who are being double-dipped by the drug manufacturers.

First, we Americans subsidize the development of medications. We then are forced to pay the higher prices for the drugs we already helped to bring to the market. This is hardly a fair deal for the American taxpayer. In essence, we have given the drug manufacturers a legally sanctioned license to price gouge the American public.

Here are just a few examples of drugs that have been developed with Federal funds: AZT, used to treat AIDS, with a price tag of $2,000 to $3,000 a year. Ceredase, used in Gaucher's disease, which costs $350,000 for the first year; Taxol, to treat ovarian cancer, at about $10,000 per year; Nicotine patches, $100 a box, which help people to stop smoking; Levamisol, at $6 a tablet, used to treat colon cancer.

The Congress provides billions of dollars each year to the National Institutes of Health [NIH] to assure that the United States is on the cutting-edge of medical and scientific advances. The finest researchers in the world work at our own laboratories here in the United States. We need them and we want their contributions.

However, it is unfair, we think, to ask NIH to also assume the responsibility of making sure that its discoveries are fairly priced for the American public. All the research in the world benefits no one if the price tags on these products are out of reach. This is why I believe, that we need a new mechanism to assure Americans that drugs that are being developed with Federal funds are priced reasonably. Just as drug manufacturers' stockholders expect a fair return on their investment, the American public should expect the same on theirs. We want a fair return on our investment.

Today, we will use drugs to treat cancer and AIDS as examples of the drugs that have been developed with substantial Federal support. In spite of these significant Federal contributions, drugs to treat these conditions have been marketed at staggering prices.

I do look forward to working with my colleagues in the Senate and the House, the officials of the administration, to develop a true and reasonable pricing mechanism. By doing anything less, we have failed as Members of Congress in our fiduciary responsibility to the American taxpayer.

Senator Cohen.

STATEMENT OF SENATOR WILLIAM COHEN

Senator COHEN. Thank you very much, Mr. Chairman.

In view of the fact that we have so many members here and such a long list of witnesses, I am going to make my remarks very brief and ask that my full statement appear in the record. I will try to at least go behind some of the statistics you will hear today.

Before I do that, I want to commend Chairman Pryor for his efforts in trying to bring some rationality to the pricing structure of medications and the pharmaceutical industry throughout this country. I think he has been out there a long time on his own, taking on an issue which was dismissed at first as being a bit too radical, until the facts started to emerge.

So I want to commend you, Mr. Chairman, for leading the effort to bring about at least some restraint in the growth of pricing of medications which are so important to our consuming public.

I receive a lot of mail on this subject matter. I want to just refer to a couple of letters I have received from people in Maine. I had a retired couple in Yarmouth who said they never thought prescription drug costs would cause them so much worry. The wife wrote me saying, "I've thought of stopping taking my drugs, as we simply can't afford the price. But I can't afford to have a stroke or shock either, so what do I do?"

I heard from a retired couple from Biddeford who indicated they spend about $700 a month on prescriptions, and their Social Security benefits don't cover that. Another woman from Augusta, ME, says she spends $550 a month on prescriptions, and that drug price increases are a vicious cycle, that drug companies seem to have a license to steal from senior citizens. I had one retired pharmacist who wrote to me saying the prescription drug prices are so high that drugs should be placed in glass showcases like jewelry or watches.

This is very strong sentiment coming from the people that we represent, because they are getting desperate. They can't afford their medications and so they are cutting back on heating during cold months, cutting back on food, cutting their medications in half or in quarter. They have a desperate condition right now.

I understand the argument that is being advanced by many of the drug manufacturers, indicating that "We are really saving you money. By developing these high-priced medications, we are saving millions of dollars that otherwise might be required by putting people in hospitals." There is some merit to that argument, but only some merit.

It seems to me it is the equivalent of someone tossing a drowning victim a lifesaver, but the rope is about 3, 4, or 5 feet too short. It doesn't reach them. If people can't afford their medications, then all of the wonderful breakthroughs that we have in scientific research is to nought.

I think, Mr. Chairman, without going any further, that your efforts in this regard have produced a reaction from many of the drug companies that they have tried to hold down their prices across the board in their product lines. That has been of some benefit, but it hasn't gone far enough.

I think this hearing is going to contribute more to understanding exactly what the Federal contribution is and what the Federal taxpayer's contribution is to the pricing of the pharmaceutical industry.

[The prepared statement of Senator Cohen follows:]

STATEMENT OF SENATOR WILLIAM S. COHEN

Mr. Chairman, I commend you for calling this hearing to review the Federal Government's role and investment in the development of new drugs. The testimony today will be very useful in determining how much money and effort the Federal Government pours into the development of new drugs and whether this Government involvement is adequately reflected in the prices that are charged for drugs once they come to market.

Every day across this country, senior citizens and families are terrorized by the high cost of prescription drugs. The elderly, families with children, and those with-

out prescription drug coverage dread going to the doctor for fear that he or she may prescribe prescription drugs they simply cannot afford to buy.

Mr. Chairman, for many years now you have been dogged in your pursuit of more reasonable drug prices, and I am pleased that this committee's efforts are starting to catch the attention of the drug companies. In response to the threat of Federal regulation of drug prices, some companies have held down their prices over their entire product line. Unfortunately, these efforts do not go far enough or translate into more reasonable drug prices for the millions of consumers who have to pay for their drugs with their own money, with ho help from Medicare or insurance.

Even though some companies are beginning to toe the line on prices, the picture of high drug prices continues to be very grim indeed. For example:

According to the Department of Labor's statistics, drug prices increased six times the rate of general inflation between 1980 and 1992.

Last year alone, drug prices rose more than four times the rate of inflation last year.

The drugs most commonly used by the elderly have jumped in price 8 to 10 times over the past 6 years. In many instances, there was no difference in the drug itself—just huge price increases for the same product.

The real tragedy is what lies behind these numbers. Let me share with you some of the people behind the statistics:

A retired couple from Yarmouth, Maine, says that they never thought their prescription drug costs would cost them so much worry. The wife wrote me saying, "I have thought of stopping taking my drugs as we cannot afford the price, but I cannot afford to have a stroke or shock either, so what can I do?"

A retired couple from Biddeford, Maine, wishes there was some relief from high drug prices. They spend about $700 per month on their prescription drugs and their Social Security check often isn't enough to cover their monthly drug bills.

A woman from Augusta, Maine, says that she spends $550 per month on prescriptions and that drug price increases are "a vicious cycle. Drug companies seem to have a license to steal" from senior citizens.

Finally, one retired pharmacist wrote to say that prescription drug prices are so high that the drugs "should be placed in glass showcases like jewelry or watches".

While Americans are digging deeper into their pockets to pay for their medications, the drug companies are reaping huge profits at the expense of the consumer—profits five times greater than the profits of the average Fortune 500 company.

Mr. Chairman, the average person in this country subsidizes the drug companies in many ways: first, through research and development tax credits and other overgenerous tax breaks given to drug companies. Second, through taxpayer subsidy of Medicaid and other Federal programs that pay for prescription drugs. Third, through funding the National Institutes of Health, which, as we will hear today, provides internal research, grants, and contracts to drug companies to develop new drugs.

In addition, our citizens pay for high drug prices through higher insurance premiums which cover the spiralling costs of drugs. Finally, the American consumer pays for high drug prices directly out-of-pocket, when he or she makes a trip to the local pharmacy.

So, the consumer is hit again, and again, and again, by high drug prices, and the American taxpayer should have some legitimate stake in what these companies are charging for medication that is so crucial to their very lives and well-being.

Today we will focus on what role the Government plays in the research of new drugs coming to market and we will question whether there is a legitimate role for the NIH or some other party to play in determining what price should be charged when the new drug comes to market. The testimony today will provide important information for our continuing debate on how best to curb the skyrocketing costs of prescription drugs.

We cannot, of course, underestimate the importance of prescription drugs and drug companies to our Nation's health care system and we must balance all of our cost containment efforts with the need to encourage innovation and development of new drugs to combat AIDS, cancer, Alzheimer's Disease and other illnesses. All the breakthroughs in medicine, however, are meaningless if major segments of our population simply cannot afford prescription drugs.

Our task will be to craft a means to curb high drug prices without impeding vital research and development efforts, and I look forward to working with Senator Pryor in aiding the millions of senior citizens who are hurt daily by huge prescription drug prices.

The CHAIRMAN. Thank you, Senator.

Senator Grassley.

STATEMENT OF SENATOR CHARLES GRASSLEY

Senator GRASSLEY. Mr. Chairman, this morning, Donna Shalala, is appearing before the Budget Committee, and Senator Bentsen before Finance. As a member of these committees, I won't be able to participate with you this morning. I am sorry I can't because obviously this is a very important issue.

We are honored to have a good group of witnesses before us this morning representing a broad perspective on the role of the Federal Government in supporting drug development. The debate over the health care costs has escalated to a fever pitch, and it is quite possible we will begin to reform our health care system in the near future. One issue that has garnered much attention during this debate is the cost of prescription drugs. Highlighting this issue is the role the Government plays in developing some of these products.

During the last decade, the National Institutes of Health have made important scientific discoveries in the area of AIDS and cancer, but due to its inability to bring these discoveries to market, NIH has entered in cooperative agreements with pharmaceutical companies. In exchange for the scientific discovery, the pharmaceutical company further develops the therapy and brings it to market. Through this public-private collaboration, a number of significant discoveries have become available to consumers, often in a relatively short period of time.

However, many individuals, both inside and outside of Congress, contend that the ultimate price of these products does not take into account the Government's scientific contribution. A parallel issue is whether the price is reasonable for consumers, especially given the consumers indirect contribution to the development of the product through their tax dollars. A number of AIDS and cancer drugs, developed jointly by the Government and private companies, are very costly. These prices have drawn attention to the role the Government should play in pricing products produced through Government support.

This morning, we will examine the role of the Government in developing some of these therapies and setting their prices. The National Institutes of Health spends approximately $1 billion on this type of intramural research. It is important to note that this is only one-tenth of NIH's entire budget. Although $1 billion is a lot of money, NIH's total budget is $10 billion of which 80 percent is devoted to extramural research in the form of grants to universities and other entities.

Although we have identified several instances of high-priced drugs produced by public and private agreements, it is not clear how widespread a problem this is. I ask how many products have been brought to market under these cooperative agreements and how many of these agreements included reasonable price clauses? It also appears that some agreements resulted in fair pricing policies. Can the pricing clause and framework of these agreements be used as models for future agreements? Before we begin to tinker with prices, let us determine the extent of this problem.

I recognize the need to provide access to important therapies at reasonable costs. But it is important to maintain the incentives to produce such therapies. During discussions of our health care system, we seem to agree that we have the most medically advanced

system in the world. Due to medical and technical innovation, we are able to save lives and successfully treat many diseases. However, we are challenged by the need to reduce reasonably priced drugs and continue to nurture innovation. Again, I thank Senator Pryor for convening this hearing to examine these issues and I look forward to hearing today's testimony.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Grassley.

Senator Kohl.

STATEMENT OF SENATOR HERB KOHL

Senator KOHL. Thank you very much, Mr. Chairman. I, too, will be brief, and I regret that I will not be able to stay for the entire hearing.

It is a very, very important hearing, and a very important moment. The American public needs to know that what we have here is a situation in which the drug industry receives considerable assistance from the Government in developing their product. Then what the public sees is that these drugs cost, by their estimate in many cases, far too much. The public also is informed that these same drugs or similar drugs are being sold for less, in some cases considerably less, in other countries.

What is the public to figure out? What are they to decide? How do they look to the Government for aid and support in seeing to it that the prices for drugs that they buy, and must have, and that in many cases for which there is no substitute, that the prices of these drugs are such that they feel that it is fair?

Everybody knows that there are many, many people in this country, perhaps a majority of Americans, who feel that the prices that they are paying for drugs are not fair. At the same time they are made aware of the fact that drug companies' profits and return on investments are among the very highest to be found anywhere.

You put one and one, and you add up two, and it doesn't make sense to many, many people in our country. It seems to me that the drug manufacturers, if they are to maintain the independence that they want and that I believe they should have, have an obligation to redefine how they are conducting their business and to satisfy both Congress, and more importantly, the American people that their prices and their profits are fair within our system.

That is the purpose of this hearing. I think it is a very, very important hearing. As Senator Cohen has said, Senator Pryor deserves great credit for having stayed with this issue and this problem through times when people were not as sensitive as they are today, particularly now that we are going to re-do our health care system. We are going to insist on trying to bring drugs to the American people at fairer prices. The question is, do we have to have the Government to control prices. The question is, do we have to have the Government to see to it that this is done?

I hope that the answer is no. On the other hand, I think it is clear that the day of reckoning has come, and something is going to be done about the prices of prescription drugs to the American public.

I am very pleased that this hearing is so well attended, that people all across the country are going to be seeing it on television,

and that we are indeed focusing on a very important problem in American society.

Thank you very much, Senator Pryor.

The CHAIRMAN. Thank you, Senator Kohl.

[The prepared statements of Senator Kohl, Senator Simpson, Senator Craig, and Senator Burns follow:]

STATEMENT OF SENATOR HERB KOHL

Thank you, Mr. Chairman.

Mr. Chairman, this hearing continues our investigation into the pricing of prescription drugs.

We have already found that drugs in the United States cost more than in other countries. Today we look at a related issue: should government control the prices of drugs developed with substantial Federal assistance through cooperative research and development agreements (CRADA's)?

We fund basic research partly because we recognize its contributions to more targeted research and development. If private industry wants to support the government's basic research efforts, why should we make that support conditional on our definition of a fair market price for resulting products?

For example, an overpriced new airplane or mainframe computer may discourage potential customers from buying. If enough businesses choose not to buy, market forces will eventually make that product less expensive.

But prescription drugs are not jet airplanes. Unregulated competition has not lowered health care costs, and it certainly has not lowered prescription drug prices.

When a doctor specifically prescribes Coumadin to a patient with an artificial heart valve, the patient really has no choice. Similarly, Taxol may be the last resort for an older woman with advanced ovarian cancer. For either of these patients, their prescriptions aren't "investments in productivity," but matters of life and death.

Unfortunately, too many prescription drugs are overpriced. Because drugs developed under CRADA's are just a small share of the market, I think that means CRADAs are not the real problem.

The problem is that Americans—especially older Americans—cannot afford to spend so much on prescription drugs.

For good reasons, we do not want to regulate the pharmaceutical industry. For equally good reasons, however, the public is not satisfied. I hope that drug manufacturers will choose to satisfy the public with justifiable prices and profits so that Congress does not have to intervene.

STATEMENT OF SENATOR ALAN K. SIMPSON

I want to thank Senator Pryor for convening this hearing today on this important and timely topic; the Federal Government's involvement in new drug research and development. In particular, the Federal Government's involvement in cooperative research and development agreements [CRADA's] with the private sector.

These agreements have come under fire over the past few months because of the continued rise in drug prices and the recent attention placed on the drug companies by both Senator Pryor and President Clinton. In addition, a growing percentage of drugs are brought into the marketplace through Government research funded by taxpayer dollars.

In fact, up to half of the most valuable AIDS and cancer drugs are developed through these taxpayer funded agreements. Once these drugs are out in the marketplace, they are priced at a cost that is prohibitively expensive for most middle-class Americans.

The Federal Government, in attempting to respond to concerns that new drugs be made available in a timely fashion and at affordable prices developed these research agreements in which Government laboratory discoveries are made available to private drug companies for further development and marketing.

These joint agreements between the Federal Government and the private sector should continue to be encouraged because they bring innovative drugs and technologies to ailing Americans more quickly than if the Federal Government pursued these reseach projects on its own.

However, drug companies should not be allowed to gouge consumers with high prices on drugs that were developed at taxpayer expense.

The challenge for policymakers is to develop an equitable policy that assures that these drugs are priced fairly while continuing to encourage cooperative ventures between the Federal Government and the private sector.

I look forward to learning about and examining the various policy options which will be presented at today's hearing. These proposals are necessary to amend the current CRADA process so that new drugs are available to ailing Americans as swiftly as possible, but at a fair price.

STATEMENT OF SENATOR LARRY E. CRAIG

Mr. Chairman, thank you for conducting this hearing. The issue of Government investment in new drug research and development is very important as the Congress continues to grapple with health care reform and getting the budget deficit under control.

While the bulk of new drug research is conducted by the pharmaceutical industry, many important discoveries have been made by the public-private partnerships created under cooperative research and development agreements or (CRADA's).

It is my understanding that cooperatives [CRADA's] focus on early research or drug-discovery activities. The Government is usually compensated for this research of the patented drug by a royalty.

The extended process of testing a compound and getting it to market is then handled by the private entity in the partnership. This early stage of research is valuable, but very dependent on the further stages of the development process which will make the product available to the public. While I feel that the Government deserves adequate compensation for its investment, we must be careful not to unbalance the process in a way that would deter private companies from participating in these cooperatives [CRADA's].

Prescription drugs have played an increasingly important role in health care. Many new drugs are being used to treat problems that previously would have required in-hospital care or surgery. While costly, these drugs are far less expensive than alternative procedures. Therefore, I am very interested in ensuring that we continue to provide incentives for new drug development and that Federal tax dollars are being spent wisely. I look forward to the testimony from our witnesses today and hope that we can gain a better understanding of this issue and ensure that the Government is getting adequate compensation for its role in the early research process of the cooperatives [CRADA's].

REMARKS BY SENATOR CONRAD BURNS

Mr. Chairman, I want to thank you for holding this hearing. It is important, in a time when we are looking at ways to cut costs, to review the investments the government is making. In particular, special care is being taken to examine health care spending.

We are all sensitive to the prices of drugs, either through personal experience, through our parents' trials, or through the stories we hear from constituents. It is clear that drug prices are higher than they have ever been. But, I think the reason we are so sensitive about the prices of pharmaceuticals, is because this is one expense that comes directly from our wallet. Most other expenses—whether they be hospital stays, doctor visits, lab procedures, or even medical equipment—are covered by insurance, and therefore the consumer rarely sees the true cost of the service. Not so for prescriptions. And so, we are looking for ways to reduce the impact on the pocketbook.

However, we're not here to look at drug prices per se. We are here to try to answer some questions. We want to find out the various ways in which the government supports new drug R & D. We want to determine whether appropriate mechanisms are in place to protect the Federal Government's investment in new drug R & D. And we need to address the whole issue of reasonable pricing. Who should set the price when the government has taken part in development? What does "reasonable price" actually mean? And what information do we need in order to establish this "reasonable" price?

These are some hefty questions to address and I look forward to hearing our distinguished panelists' opinions of how we can tackle this issue. Let me note though, that we are not here to set a new policy; we are just gathering information.

I think Congressman Ron Wyden hit the nail on the head in his testimony on January 25 before the Subcommittee on Regulation and Business Opportunities and Energy. He said, "Americans want new cures for dread diseases on the market as quickly as possible. Americans feel just as strongly that those cures must be affordable." In other words, people want it good, fast and cheap. But we all know, in health care you can only have two of the three. If we have high quality care and instant access, it will be expensive. If it's inexpensive and fast, the quality may suffer. And if we have high quality and inexpensive, we will have to wait. The way

things are now, we have the highest quality health care system and instant access. . . . which means we have to pay dearly.

Now this does not necessarily apply to the drug industry since drugs go through extensive review processes before coming to market. And this is another problem we wrestle with . . . drugs here take an average of 13 years to get through approval as opposed to 9 years in other countries. It's my understanding that of the last 97 new drugs to come to market worldwide, 47 of them (48%) originated in the United States. I hardly think we want to discourage research and development in this country when we are the world's leaders. Sometimes this comes at a cost. The cost of developing a drug these days is in excess of $400 million.

Along those lines we have to question whether allowing the NIH to set prices will be a disincentive for private companies to enter into research and development agreements with the government. After all, their costs need to be recouped. And not all pharmaceutical companies have the strength and success of past products to help carry their research costs. As we will hear from the biotechnology folks, many companies rely on private investment to sustain research and development. They need flexibility, especially on introductory products, to attract investment and recoup costs.

But that is what we are here to find out and discuss. I want to commend the Chairman for bringing together such experts in this field and applaud you, Mr. Chairman, for your efforts to control costs in health care. I don't know one meeting in my state that I've been to recently that health care didn't come up as a concern. We have a lot of areas to examine, and pharmaceuticals are just one small part.

Thank you Mr. Chairman and thank you, distinguished guests, for taking time to come meet with us.

The CHAIRMAN. Senator Durenberger.

STATEMENT OF SENATOR DAVE DURENBERGER

Senator DURENBERGER. Mr. Chairman, thank you.

The problem is not just prescription drugs, obviously. I went through a little neighborhood drugstore in Minneapolis a couple of weeks ago, and a woman recognized me right away—one of the salespeople—and took me over to where I could find some nighttime cold remedy. Then she proceeded to explain how increasing numbers of older people in that neighborhood were coming and going down the aisle, looking around, and knocking a box into their purse. Mr. Chairman, I think this is an incredibly important problem, and the leadership role that you are playing is very significant.

The suggestion that you've done this alone is not quite accurate. I think at first you were alone on your solutions, at least in the leadership role. But the minute the Good Lord came at your health habits with that little heart attack that you had, I decided that this issue should not be partisan. It should not be left to you as a Democrat to carry the only lead in pointing to the problem.

Back in May of 1991, I went to the floor and made an impassioned statement, and got all the same kind of reaction from people that you did. I think this first point is that this is not a partisan issue. but I must also say that it ought not to be what I'd call a "60 Minutes" kind of an issue.

I know it is important to have all this stuff up here on the tables, with all these prices on them, and to do all these dramatic illustrations of this sort of thing. But that is the problem with the way we make policy in this country. If you go to the average senior citizen now when they are going to see a new doctor, the first thing the doctor says is, "Go back to your medicine, or your medicine cabinet, take all your pills and put them in a bag and bring them in so I can see how other people have been diagnosing your health."

They have a fancy name for this process, but that is kind of what goes on. You look in the average medicine cabinet, or whatever you call it, in your home State, for the average person who has lived a while, and you are going to see row after row of a variety of all kinds of things.

I venture to say, Mr. Chairman and my colleagues, that is the condition that health policy is in this country right now. We have a whole lot of often conflicting policies running into each other that have been made because of some dramatic problem, or some ill-directed solution.

I appreciate the opportunity to be on this Committee to deal with this particular issue, but I'd also caution all of us to keep our eye on the main goal, which is to find a better way for public policy to bring the best of American technology to Americans.

I have to leave, too, as others do, to go to two of the five health committees that I am on. I am going to go to the Finance Committee; and I am going to go to the Labor and Human Resources Committee. I also went to my first meeting yesterday of the Board of Technology Assessment. I consider this an important health committee.

So, here is one Senator sitting on five health committees—I'm on the Environment and Public Works Committee, too; I consider that a serious health committee—making all kinds of policy. In the House, there are probably twice as many committees doing the same sort of thing. I guess my bottom line is to express my appreciation, as others have, to you, Mr. Chairman, for your leadership, and to caution all of us to keep our eye on a particular goal, and to try to work toward that without the conflict that so often comes into the way we make policy.

The CHAIRMAN. Thank you, Senator Durenberger.

Senator Shelby.

STATEMENT OF SENATOR RICHARD SHELBY

Senator SHELBY. Thank you, Mr. Chairman.

Mr. Chairman, I will join the chorus and thank you for your leadership in this area, and also the work of your staff. You have an outstanding staff here.

Mr. Chairman, I am sure that everyone here realizes that the work we are undertaking today is not a trivial matter, but it is very important to our efforts to reform the health care system in this country. It is for these reasons that I am also sure that most people realize that the audience that you will be addressing today is much larger than the members of this Committee, since both Congress and the rest of the Nation will be listening intently to what you have to say about these problems.

We also realize that the seniors, who comprise only 12 percent of the population, consumed 32 percent of the 1.5 billion prescriptions written in the 1980's. That figure has increased now. I am also sure that given these statistics it is not difficult to imagine the tremendous price tag associated with obtaining medication—in other words, staying alive. Moreover, it is not difficult to imagine the tremendous financial burden this creates for people on fixed incomes.

I truly believe, Mr. Chairman, that drugs are a very cost-effective part of health care, an integral part of health care. A properly prescribed drug regimen can prevent the onset of serious illness, and can often prevent hospitalization, which saves money and allows us to stay healthy. But soon many elderly individuals in this country will be completely priced out of the market.

I am also aware of the over-the-counter drugs, and how they have risen in price continuously. I don't know the answer to this problem, for there are no easy solutions.

Mr. Chairman, I also have two other committees, as do most of my colleagues. I have Energy and Banking, and the Energy Committee is also meeting this morning. I regret that I will not be able to remain here to listen to all of the distinguished witnesses; however, I will stay to hear the testimony of my young colleague, Congressman Wyden.

[The prepared statement of Senator Shelby follows:]

PREPARED STATEMENT OF SENATOR RICHARD SHELBY

Mr. Chairman, I want to commend the staff and you for all of the work that has been done in preparing for today's hearing. I also would like to thank the distinguished panel of witnesses for coming forward to provide this Committee with some valuable insight as to the nature of the problem before us. Hopefully, this hearing will help us to identify ways to ensure that prescription drugs developed with substantial Federal involvement or through a cooperative research and development agreement (CRADA) will be priced reasonably and fairly.

It also is appropriate that this Committee should hear the experts address these problems and determine what actions can be taken at the national level to reduce the high cost of prescription drugs which substantially and disproportionately impacts the elderly. In November, I addressed a group of retired teachers in my state who told me that they were paying more for their prescriptions, but getting less medication. Obviously, this is a situation about which they are not too happy.

Many senior citizens are not limited to just one medication, but are often taking several drugs at one time. For example, approximately 6.7 million Seniors are taking three or more prescription drugs at one time, and one-third of the patients in nursing homes receive eight or more drugs daily.

Also, we know that Seniors over age 65, who comprise only 12 percent of the population, consumed 32 percent of the 1.5 billion prescriptions written in the mideighties. I am sure that this figure has increased now; however, given these statistics, it is not difficult to imagine the tremendous price tag associated with obtaining medication. Moreover, it is not difficult to imagine the tremendous financial burden this creates for persons on fixed incomes.

I truly believe that drugs are a very cost-effective part of health care. A properly prescribed drug regimen can prevent the onset of more serious illnesses and can often prevent hospitalization. But soon many elderly individuals will be priced out of the market.

I am sure everyone here realizes that the work that we are undertaking today is not a trivial matter, but is important to our efforts to reform the health care system in this country. For these reasons, I am also sure that you realize that the audience that you are addressing is much larger than the members of this Committee, since both the Congress and the rest of the Nation will be listening intently to what you say today.

I urge you to the extent possible to simplify your explanations. The average American needs to understand why the cost of new drugs is quite large, while at the same time, the price of basic headache medications that have been around for years is also increasing. I realize that there may not be simple answers to these problems. However, we have an obligation to find effective solutions since that is what the American people expect us to do.

The CHAIRMAN. Thank you, Senator Shelby.

I believe next is Senator Feingold.

STATEMENT OF SENATOR RUSSELL D. FEINGOLD

Senator FEINGOLD. Mr. Chairman, I congratulate you on holding this hearing, and your work in this area. I have no formal statement, other than to say in my 10 years as chairman of Wisconsin's Aging Committee on the issues you raise with regard to prescription drugs, and related issues, frequently came up. I look forward to hearing from the experts on the issue.

The CHAIRMAN. Thank you, Senator Feingold.

I don't know if in Wisconsin they tried to abolish the Aging Committee, there or not, but they are going to try that today on the Senate floor. That is why we are going to hold our witnesses to 4 minutes each, because Senator Cohen and I, and other members of the Committee, have to go and defend this Committee and its work. We think that we can do it with, hopefully, success, with the support of our Committee members.

Congressman Wyden, we appreciate your attending. You are our first witness. You have done great work in this field, and we will now give you the floor.

STATEMENT OF HON. RON WYDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WYDEN. Mr. Chairman, thank you, and I ask, too, that my statement go into the record.

Frankly, the statements that I have heard by you and your colleagues on the Aging Committee strike as a darn good reason why so many of the senior citizens and their advocates want to see your committee reauthorized and preserved. This has been your fight and what you have done on this issue is a perfect example of why the Committee needs to be reauthorized.

Let me make just a couple of comments and if there is time for questions, I will be happy to take them.

I think it is quite clear that a growing amount of pharmaceutical research in this country is essentially fail-safe for the drug companies. What you have is a situation where the taxpayer bears the risk and the companies walk away with the profits. In many of these instances what we have seen is that they are essentially offering the judgment that they are playing the role of Louis Pasteur, of the scientists making the intellectual contribution, when in fact their primary activity is to market the taxpayer-funded discoveries with salesmanship.

What I'd like to do is talk about the two essentially no-toll freeways to the market that are now being paved with taxpayer money. The first is through a direct partnership between the Federal Government through a Cooperative Research and Development Agreement. The second route is for manufacturers to partner with a university or private research group.

A quick example of each: the Taxol case that you mentioned is one I have been looking at. The Federal Government discovered and developed this drug at the National Cancer Institute. I was told that in a letter, in which the Government said that it, in effect, discovered and developed—not partially developed; totally—discovered and developed this drug. The Government did all this and produced Taxol at a cost of $0.60 to $0.90 per milligram. But the retail price that has been worked out between the Government and Bris-

tol-Myers Squibb has the public paying $4.87 per milligram of Taxol, even though the Government discovered it and developed it.

Now, the Government made two mistakes in that deal. First, price was an afterthought. After the deal was negotiated and the Government lost its leverage, then the Government started talking about price. That was mistake No. 1. Mistake No. 2 is that the Government looked at a median price list of what they thought were existing cancer therapies. The problem was that an unrelated drug, a human growth hormone drug, got on the list. That jacked the price up. If you had just cancer drugs on the list, not human growth hormones, the price would have been 40 percent less.

So Taxol is a current example of how under these cooperative agreements, where the taxpayer bears the risk and the company gets the profits, are breaking down.

The other example that I wanted to offer real quickly, Mr. Chairman, involves a truly outrageous agreement that has been entered into between Sandoz, a Swiss pharmaceutical corporation, and the Scripps Research Institute in southern California. Under this, Scripps has been getting 75 percent of its operating money from grants from the Federal Government. The public's investment in Scripps amounts to nearly $100 million a year.

Under this agreement over the next 10 years Sandoz is going to get the right of first refusal to essentially all this research for $300 million. This is what amounts to a publicly financed leveraged buy-out of taxpayer-funded research.

Now, Scripps may have a constitutional right to become a Sandoz lab, but Scripps has no right to make Sandoz the American taxpayers' favorite charity.

I read in the newspaper that on this deal, where over 10 years and $1 billion worth of federally funded research is going to be made available, not only did the Government not approve it, not only did they not take steps to explore it, but according to Scripps, they had absolutely no contact with the National Institutes of Health.

I know my time is up. I've asked the National Institutes of Health to investigate this and other deals. We have been told that Scripps is not cooperating in terms of furnishing this information. If that is the case, Mr. Chairman, I would propose that Federal funds be withheld from these organizations until they actually furnish these agreements so we can see how the taxpayers' interest is being protected.

I look forward to working with you on legislation to correct this. My own view is that what we have to do is agree that a pricing strategy has got to be entered into up front, rather than as an afterthought, and look to put more competition into these deals.

[The prepared statement of Congressman Wyden follows:]

PREPARED STATEMENT OF REPRESENTATIVE RON WYDEN

Mr. Chairman, it's a pleasure to be before your Committee, where you have led the fight so often for a fair shake for seniors and all Americans. I appreciate the opportunity to share with you the findings of my own investigation into an additional source of subsidy to the pharmaceutical industry: taxpayer-supported research and development. Independent experts report that up to half of the most valuable cancer and AIDS drugs are developed with taxpayer support, putting into play billions of dollars of Federal research dollars and corporate profits.

The fact is that a growing amount of pharmaceutical research is fail-safe for the drug companies: the taxpayer bears the risk, and the companies walk away with the profits. Several major companies assert they are modern day Louis Pasteurs advancing the cause of science, when in fact their primary activity is to market taxpayer-funded discoveries with super-salesmanship. Too often, when Federally funded research labs negotiate with these salespeople in white coats, taxpayers and consumers are left out in the cold.

At present, drug companies have their choice of two no-toll freeways to the market, both well-paved with tax dollars. The first is to establish a direct partnership with the National Institutes of Health, by entering into a Cooperative Research and Development Agreement, or CRADA. A second lucrative route is for the manufacturer to partner with a university or private research institute that has received no-strings funding from the NIH. Let me briefly offer the Committee an example of each.

Taxol, a drug described by the National Cancer Institute as the most promising anti-cancer agent developed in the past 15 years, is a revealing case study of CRADA partnerships in action. The fact is that NCI and the taxpayers did all the heavy-lifting necessary to get Taxol to market. According to a September 10, 1991 letter I received from Cancer Institute Director Dr. Broder, "Taxol was discovered and developed within the NCI's comprehensive anticancer drug development program."

Specifically, Dr. Broder stated, the NCI was responsible for—"(1) the initial collection and recollection of [Pacific Yew tree] bark; (2) all biological screening in both cell culture and animal tumor systems; (3) chemical purification, isolation, and structure identification; (4) large-scale production, from collection of bark through preparation of material suitable for human use; (5) development and production of a suitable intravenous dosage formulation; (6) preclinical toxicology; (7) filing of an Investigational New Drug Application (INDA) with the FDA, along with all required documentation; and (8) sponsorship of all activities, including efforts directed toward total and partial synthesis of the drug, have been supported through NCI research grants and intramural programs."

Mr. Chairman, the government did all this and produced Taxol at a cost of 60 to 90 cents per milligram. But the retail price worked out between NIH and the government's commercial partner, Bristol-Myers Squibb, has the public paying $4.87 per milligram of Taxol.

This very high price is the result of two significant mistakes NIH made in negotiating the final price of Taxol. First, price was an afterthought in the negotiations. NIH settled on Bristol-Myers Squibb as their partner before they even discussed price. I think you will agree that the time to negotiate something this important is *before* closing the deal, not afterwards when the Government has lost its leverage.

The second crucial error made by NIH was their agreeing to a price set at the median of prices for existing cancer therapies. The median isn't necessarily a bad idea, because many new drugs are priced above all existing therapies, as your Committee staff reports have shown. But the list of existing cancer therapies NIH used to find the median included an unrelated product, Human Growth Hormone (HGH). If HGH had been left off the list, consumers—chiefly elderly women—would pay 40 percent less for Taxol.

Taxol shows the shortcoming of the CRADA process under existing law. But the evidence indicates that the taxpayers may be exploited far more aggressively through biomedical partnerships lubricated by taxpayer dollars. My investigators have found perhaps the premier example of this immense class of hidden subsidies is the long-term agreement recently entered into between the Sandoz Corporation, a major pharmaceutical company based in Basel, Switzerland, and the Scripps Research Institute. Scripps gets 75 percent of its operating funds from grants from the NIH and other Federal agencies. The public's investment in Scripps amounts to nearly $100 million each year.

Under this agreement, and in return for approximately $300 million from Sandoz over 10 years, Scripps will give the drug company rights to commercialize any or all of its research beginning in 1997. This has been appropriately characterized as a leveraged buy-out of a $1 billion taxpayer investment for $300 million.

Now Scripps may have a constitutional right to become a Sandoz laboratory, but Scripps has no right to make Sandoz the American taxpayer's favorite charity. In fact, what is most troubling about this deal is the fact that the Government had no say in it. It is my understanding that no prior approval from NIH was required for Scripps to commit public resources to Sandoz. According to published comments by a Scripps vice-president, "There is no process for contact with NIH over this type of matter. They must be aware of the [Sandoz agreement] because they read the [newspaper accounts], but *there was no formal contact.*" [emphasis supplied]

Mr. Chairman, my inquiry has found evidence that Scripps and research organizations like them may be "patent machines", in which officers in a tax exempt research institution that holds patents may also have a significant interest in a for-profit company that benefits from the licensing of these new technologies. The question is: is the public interest protected in a back-room deal approved by a handful of corporate executives?

At my request, NIH Director Bernadine Healy recently initiated a review of agreements between drug and device companies and NIH-funded universities and private research institutes. These deals have been negotiated in the dark, out of the public view, and I'm going to do everything I can to shed light on them.

In addition, this morning's Washington Post suggests that Scripps may be stonewalling and refusing to hand over copies of the agreement. If this is true, I propose that all further Federal funds be withheld pending the production of all relevant documents related to this deal. Mr. Chairman, those spending the taxpayer's money must be accountable.

The Taxol case and the Scripps-Sandoz deal are recent examples of how the public gets bumped twice for cash, once when taxpayers finance the basic research, and again when the resulting product is priced at sky-high levels.

With this in mind, I said Monday that I will be shortly introducing legislation [1] to ensure that taxpayers can afford the products created from their investments in biomedical R&D. Under my proposal, the Federal Government and its grantees would be obliged to negotiate a pricing formula before entering into the agreement. At present, prices are discussed only after a commercial partner has closed a deal to cash in taxpayer funded research—at a point when the U.S. Government has lost all of its leverage to obtain fair prices for our consumers.

The bill would also discourage the routine practice whereby NIH and NIH-funded research organizations grant exclusive agreements with a single drug company. Instead, more than one company might be co-licensed to develop the product, to ensure a greater level of price competition in the market.

To enforce my proposal, the pricing and royalty provisions of these contracts would permit the revocation of the exclusivity provisions, and allow for the disbarring of an offending company from future agreements for at least five years.

I strongly support President Clinton's technology transfer initiative, and in fact authored the Federal law establishing pilot projects to promote technology transfer between Federal labs and small business. It is especially important, however, that biomedical technology transfer meets high standards, because 35–40 percent of all drug sales are paid for by public programs like Medicare and Medicaid. For the public to tap the full potential of technology transfer, commercial partners must provide a greater return for the taxpayers' investment.

The CHAIRMAN. Congressman Wyden, thank you.

I just have one question, and it is on Taxol. If you maintain that the Government discovered Taxol in Federal research labs, and Bristol-Myers Squibb came away with the product, what did the Government get out of this?

Mr. WYDEN. What the Government essentially got was the right to have Taxol marketed quickly. We all commend Bristol-Myers Squibb for doing it, but when you look at the long list of functions that the Federal Government performed, what you are left to ask is exactly what did Bristol-Myers Squibb do other than put this in a pretty little box and send it out all over America?

Dr. Broder essentially itemizes, and I have it in my testimony, what the Federal Government did, and it is quite clear to me that the taxpayer did the heavy lifting.

The CHAIRMAN. Senator Cohen.

Senator COHEN. In your prepared statement when you talk about establishing a price review board, would you have this board oversee the pricing structures of those drugs developed through cooperative research agreements, or for all prescription drugs?

[1] Note: Introduced as H.R. 1334.

Mr. WYDEN. Senator, I think you have the wrong witness. I have not been the one who has been calling for a price review board. A number of our other colleagues have.

What I am calling for is a change with respect to these CRADA's and cooperative biomedical partnerships, first where there is a pricing strategy agreed to up front, and second where the Government looks to get more bidders involved.

Senator COHEN. In some of the statements that you have made in the House you had advocated that, so we will look to see what other colleagues of yours are suggesting.

That is all I have, Mr. Chairman.

The CHAIRMAN. Senator Durenberger, do you have any questions?

Senator DURENBERGER. Just a compliment to our colleague from Oregon, who is such a terrific pioneer and advocate of health policy.

The CHAIRMAN. Thank you.

Senator Shelby.

Senator SHELBY. Thank you.

What type of data, Congressman Wyden, from NIH and the companies involved should be used to determine the reasonable and fair price? Have you gotten into that?

Mr. WYDEN. I think that is the key question. Obviously we want to give the Government a lot of flexibility as it approaches this pricing question. We would want to look at the risk to the company in terms of what they are going to have to put out. We want to look at how long it would take a drug to get commercially approved. In the Taxol case, it was approved very quickly.

But what we really want to do as we try to promote these partnerships, and we have said we want to do it, is try to make sure that the companies, if they are carrying a lot of risk, get rewarded. But if they aren't then we make sure that the taxpayer gets some break on price.

Senator SHELBY. You want to make sure the taxpayer is not raped in this deal.

Mr. WYDEN. You put it graphically.

Senator SHELBY. That is right.

At what point does the Federal Government's investment in the research and development of a drug trigger the Government's involvement in determining the price of the drug?

Mr. WYDEN. The Government is in effect inviting the partnership in these areas, in AIDS and cancer, where we want to move very quickly. That is a good idea. I think when there is an effort to enter into one of those agreements, it ought to be determined right up front that the Government isn't just going to say price is an afterthought. We ought to look at price at the outset. As I say, this is going to require some flexibility.

We know, for example, that there may be fruits of some of this research that hasn't even come into existence. There is intellectual property that won't even exist when a Scripps or other organization undertakes its research.

All I am saying is that we have to look at the ramifications at the outset rather than to essentially play catch-up ball when all

the folks are writing Chairman Pryor and are unhappy about their prices.

Senator SHELBY. Do we have the right personnel in place to negotiate from a flexible position on this with the drug industry?

Mr. WYDEN. I think clearly, if this becomes a priority function to address these price questions at the outset, we can do it, especially if the Congress doesn't micromanage this formula. I am saying that we ought to look to flexible pricing formula that looks at risk, the time for getting drugs approved, these kinds of considerations, and that ought to be done at the outset.

Senator SHELBY. The Government is going to need top-notch negotiators to do that, who know what money is, and not give it away early, right?

Mr. WYDEN. The Government is going to have to understand that it is dealing with business people and taxpayer assets, that is correct.

Senator SHELBY. It is my understanding that Merck, and other companies—I just mention Merck since it is big and very successful—have generally not entered into CRADA's, because of concerns over pricing clauses. Is this true?

Mr. WYDEN. I know you will hear from the NIH. They will give testimony indicating that that has been the case. But we know that there are some drug companies that today are essentially focusing on sales and marketing and distribution. Those are the ones that I think we particularly have to watch here because they are trying to harvest the fruits of the taxpayer-funded research. Then there are others that focus more on trying to develop the intellectual product.

All I am saying is that if they have in fact taken the risk to develop the intellectual product, let's reward them; but when they haven't, and when the taxpayer has in effect carried the risk, that ought to be considered in the price.

Senator SHELBY. In the case of Sandoz and Scripps, do you have any information as to whether or not Scripps offered this deal to some domestic pharmaceutical manufacturers before it offered it to a Swiss company, thereby using taxpayers' money again to subsidize a foreign company?

Mr. WYDEN. I don't know that at present.

Senator SHELBY. You see what I am getting at?

Mr. WYDEN. Absolutely. We have made that point as subtly as you have, I'd point out. It is an incredible thing to think that a Swiss pharmaceutical corporation is given the right of first refusal to what amounts to $1 billion of Federal research and the Federal Government hasn't even been informed.

If Scripps is not cooperating with the National Institutes of Health, which is what I have been told by several at NIH, I think we ought to cut off their Federal funds at this point, until they hand over those documents.

Senator SHELBY. Congressman, have you been involved in research with NIH and its agreements with various medical schools doing bio-medical research? If so, what happens to those findings which are basically funded with taxpayer money when the universities are dealing with foreign companies, too? This issue is not exactly the same, but there is some overlap.

Mr. WYDEN. It certainly does. It is part of our inquiry. I have asked Dr. Healy at the National Institutes of Health, to try to gather all of the contracts that have been entered into between NIH and these various research operations in universities and drug companies. I suspect that we are going to find some very, very interesting things as we collect those contracts.

Senator SHELBY. Thank you, Congressman.

The CHAIRMAN. Ron, we want to thank you.

Let me say, for the record, so all of our listeners might know, we have used the word CRADA two or three times here. I must say I am trying to become educated in this field. That is the cooperative research and development agreement. Those agreements, I assume, are entered into by the Federal research facilities and the private drug industry. I think we are going to be hearing a lot about those in the future.

Mr. WYDEN. I appreciate your making that clear, Mr. Chairman, because I was skipping fast. There are essentially two no-toll freeways to the market that are paved with tax dollars. One of them is these cooperative agreements that you described, and the other is the kind of Scripps/Sandoz bio-medical partnership deals that have gotten so little oversight.

The CHAIRMAN. Congressman Wyden, we thank you for appearing today. We thank you for your contribution.

Mr. WYDEN. Win that fight today.

The CHAIRMAN. Thank you, sir. We are going to be there trying.

We will call our first panel now. We have Caroline Decker, Derek Hodel, Jamie Love, and Ralph Nader.

Caroline Decker is a social worker with the Jefferson Comprehensive Care in Arkansas. She works with AIDS patients throughout the Arkansas AIDS Foundation. Caroline, we welcome you.

Derek Hodel is no stranger to this Committee. He is with the AIDS Action Council. This group represents people with AIDS. It deals with issues involving AIDS treatment.

Ralph Nader, who started the Taxpayer Assets Group. This group is doing research on the whole issue of how the Federal Government supports the development of breakthrough drugs.

Caroline, we will start with you. Once again, if you would assist us by trying to cooperate with the 4-minute rule, then we will follow with questions, and your full statement will be placed in the record.5

STATEMENT OF CAROLINE DECKER, ARKANSAS AIDS FOUNDATION, LITTLE ROCK, ARKANSAS

Ms. DECKER. My name is Caroline Decker. I am a social worker who works directly with people living with HIV and AIDS.

I have a big challenge today. I must somehow express to you how much importance this issue of overpriced pharmaceutical drugs has. There is not a day that goes by when I do not address this situation.

A typical situation is the following: I get a phone call from the patient or the hospital or the doctor. The question is, "Can you help this person find resources to buy, or help them pay for, their medi-

cations? They do not have enough money for them." Then I struggle to find resources.

I want you to understand that there are programs out there that try to help pay for the medications. I am working with one of those right now. But there is no way each program can help everyone that is in need.

When one discovers they have a terminal illness, of which AIDS is one, you try to seek solutions and hope. Medications are hope, but when you find you cannot afford the medications, or you know you will be broke in a year if you buy the medications, hope again is thrown out the window. Again, the person is going directly into a dead-end.

When the resources fail, I am the one left to offer the person something less than what they really need, which is the medication. I am here today to ask you to lift this burden off of me.

Thank you.

[The prepared statement of Ms. Decker follows:]

STATEMENT OF CAROLINE DECKER

I come to you today to present the personal aspects and the effects the over priced pharmaceutical drugs play on people living with HIV/AIDS. My name is Caroline Decker and I am a social worker who works directly with people living with HIV/AIDS. Every week that goes by I must scramble to help someone try to find resources to pay for the drugs that are supposed to keep them alive. For example, one evening I got a phone call from a family that had just found out their adult child was diagnosed with AIDS. The patient was being released from the hospital and prescribed a couple of medications. The family was shocked when they discovered the price of only one drug the patient needed to take would cost them $600.00 for one month's supply. This situation is a weekly scenario in which I must help these people come up with resources to help pay for the drugs. Another example, is one dear person we shall call Tom. Tom was diagnosed in 1987 with AIDS. He decided to try the AZT trails which at that time cost over $1,000 for a one month supply. By the end of one year he had lost his insurance, his job, and was completely broke from the medical and drug bills. If it had not been for support from friends, welfare, and survival techniques, he would be dead today. These survival techniques are used when the person learns to find drugs from underground systems, other people who cannot take the drugs that are needed, or learning to rationalized the drugs each month. For example taking only two instead of three a day. Another example is the ones that just give up and don't even take the drugs. The price of the drugs are beyond their income, so is not even included in their budget. The prescriptions are usually thrown into the trash can. One woman told me that if she was not on a program that helped pay for her AZT she would not be taking it. "There are too many other things I need to buy such as food, before I would buy any AZT."

I do know there are programs out there through the pharmaceutical companies that help indigent patients. These programs do help somewhat. There are many guidelines and rules to the programs. Such as the company will only supply for six months and it usually takes up to six weeks to be approved for the program. Most people cannot wait for six weeks to be approved. If they are sick now, they need the medicine now!

I urge you to address this critical situation. I know I have only mentioned the effects the rising cost of medication plays on the ones that are sick but, I feel the result of this problem is death. Death that could have been avoided or perhaps a life prolonged for a significant amount of time. There is a solution to the overpriced pharmaceutical drugs and I hope it will start today.

The CHAIRMAN. Caroline, thank you very much.

Mr. Hodel.

STATEMENT OF DEREK HODEL, DIRECTOR, TREATMENT AND RESEARCH ISSUES, AIDS ACTION COUNCIL, WASHINGTON, DC

Mr. HODEL. Thank you, Mr. Chairman.

Good morning. My name is Derek Hodel, and I am the treatment issue director at the AIDS Action Council. The council represents over 900 community-based organizations around the country that provide care and advocacy for people living with HIV or AIDS.

Almost without exception, AIDS drugs are very expensive. But excessive pricing of those drugs for which the Government has made development contributions is but the most egregious example of the fundamental flaws inherent in our overall health care delivery system, flaws that pertain to prescription drugs in general.

As I am sure this Committee is aware, approximately 40 percent of people with AIDS become impoverished as a result of their health care expenses, and come to rely on Medicaid. It is important to remember that exorbitant prices for drugs produced with Government assistance are hardly unique. Profit margins for the industry have consistently been higher than other industries. The prices for prescriptions drugs have consistently risen faster than inflation. Likewise, citizens of the United States have consistently paid far more for prescriptions drugs than citizens of other countries.

No one questions the desperate need to develop AIDS drugs, nor do they question the need to find the most humane and efficient way of providing what few drugs exist to those in need. The question is how to do both at the same time.

In the United States, unlike any other country in the industrial world, we grant significant monopoly protections in the forms of patents and other exclusivity provisions to manufacturers, who then charge what the market will bear. This protected free-market approach leaves consumers particularly vulnerable.

The pharmaceutical industry has historically justified high prices and the high profit margins they enjoy by claiming proportionally high research and development costs. Even the suggestion of price regulation is presented as a threat to innovation.

For people with AIDS, many of whom follow every research development with barely restrained hope, this charade is not only deceitful, it is heartless. It is time for people with AIDS, and for the American consumer at large to confront this veiled threat. We can no longer afford to be held hostage by an avaricious industry.

I am struck by how long we have engaged in this debate. In 1938, when the FDA Act was passed by Congress, the industry argued it would cripple research and delay getting drugs onto the market. Nevertheless, the 1940's and 1950's proved to be the golden age of pharmaceutical innovation, and profits soared.

In 1959, Senator Estes Kefauver held hearings which documented above-average profit levels, a lack of price competition within the industry, huge markups, and inordinate spending on promotion. Sound familiar?

In response, the industry claimed the Kefauver-Harris amendments would cripple research and disable innovation. Although drug development did become markedly more expensive, profits did not seem to suffer.

AIDS has spurred an unprecedented cooperation between industry and Government. Through the NIH we spend over $1 billion per year on AIDS research, much of it on clinical evaluations of drug treatments. The AIDS clinical trials group is among the larg-

est clinical trials networks in the world, and yet AIDS drugs remain among the most expensive drugs on the market.

AIDS has also prompted dramatic reforms of the drug approval process. The FDA has significantly streamlined its review process, cutting years off the time required for a drug to come to market, and has implemented innovative conditional approval mechanisms that permit companies to market drugs following only preliminary proof of efficacy. Yet AIDS drugs remain among the most expensive drugs on the market.

Mr. Chairman, it is time that pharmaceutical prices in the United States are intelligently restrained, as they are in almost every other developed country in the world. We believe that this is an appropriate role for the Federal Government to perform, and urge that such a regulatory function be incorporated within whatever health care package Congress ultimately adopts. Certainly a price review board on the Canadian model would be well worth exploring.

Further, we would oppose imposing such a role on either the NIH or the FDA. These agencies have historically, and appropriately, avoided questions concerning health care economics. The regulation of research, safety, and economics must remain distinct.

Finally, it is imperative that with respect to price regulations, the marketplace be treated as a whole. The regulation of any one segment of the market, whether orphan drugs or CRADA drugs, must occur in the context of overall price regulation. To regulate only isolated markets segments will further distort the market and could serve as disincentive for manufacturers to participate in these worthwhile programs.

Mr. Chairman, I commend you and your staff for your tenacity with respect to the issue. I urge you, as you continue to examine the issue further, to press for the inclusion of prescription drug pricing regulations in our final health care package of reforms.

Thank you again for the opportunity to testify.

[The prepared statement of Mr. Hodel follows:]

Testimony of Derek Hodel, Treatment Issues Director
AIDS Action Council
24 February 1993

Good morning. My name is Derek Hodel, and I am the treatment issues director at the AIDS Action Council. The Council is the only national organization dedicated solely to shaping federal AIDS policy. My remarks today are on behalf of over 900 community based organizations around the country that provide care and social services to, and advocate for, people living with HIV or AIDS. It is a privilege to be here.

The questions before us today concern the federal contribution toward the development of AIDS drugs, and ask, implicitly, whether such contributions yield a sufficient payoff. Almost without exception, AIDS drugs are very expensive. But excessive pricing of those drugs for which the government has made substantial development contributions is but the most egregious example of the fundamental flaws inherent in our overall healthcare delivery system, flaws that pertain to prescription drugs in general.

Of course, if we pay dearly to develop a drug (as we do with most AIDS drugs, many of which are researched at the NIH) it is particularly troublesome to then pay again through outrageously high prices. Both times around, these are costs that ultimately are borne by the taxpayer. As I'm sure this committee is aware, approximately 40% of people with AIDS become impoverished as a result of their healthcare expenses and come to rely on Medicaid. But it is important to remember that the prices for drugs produced with government assistance are hardly an exception to the rule. Profit margins for the industry have consistently been higher than other industries. The prices for prescription drugs have consistently risen far faster than inflation. Likewise, citizens of the United States consistently pay far more for prescription drugs than citizens of other countries.

No one questions the desperate need to develop drugs to treat AIDS, nor do they question the need to find the most humane and efficient means of providing what few drugs exist to those in need. The question is how to best do both at the same time. In the United States, our system is unlike any other in the industrial world -- we grant significant monopoly protection, in the form of patents and other exclusivity provisions, to manufacturers who then charge whatever the market will bear. This "protected free-market" approach leaves consumers, who are generally in no position to shop around, particularly vulnerable. People with AIDS have shown repeatedly that they will go to great lengths to attain treatments they need. As I have testified previously before this committee, this includes importing medications from abroad, where prices are often substantially lower.

The pharmaceutical industry has historically justified high prices, and the high profit margins they have long enjoyed, by claiming proportionally high research and development costs. Even the suggestion of price regulation is presented as a threat to innovation. For people with AIDS, many of whom follow every research development with barely restrained hope, this charade is not only deceitful, it is heartless. It is time for people with AIDS, and for the American consumer at large, to confront this veiled threat. We can no longer afford to be held hostage by an industry concerned only about its bottom line.

As I prepared for today's hearings, I was struck by how long we have engaged this debate. In 1938, when the Food Drug and Cosmetic Act was passed by Congress, requiring the FDA for the first time to approve drugs on the basis of safety criteria, the pharmaceutical industry argued that such measures would cripple research and delay getting drugs to the market. Nevertheless, the 40's and 50's proved to be the golden age of pharmaceutical innovation, and profits soared. In 1959, Senator Estes Kefauver held hearings which documented above average profit levels, a lack of price competition within the industry, huge markups, and inordinate spending on promotion. The Kefauver-Harris amendments required FDA for the first time to consider efficacy in the approval of drugs, a move the industry bitterly claimed would cripple research, and disable innovation. To be sure, drug development became markedly more expensive. Profits, on the other hand, did not seem to suffer.

With AIDS, the demand for drugs has spurred unprecedented cooperation between industry and government. Through the NIH, we spend over $1 billion per year on AIDS research, much of it on clinical evaluations of drug therapies. The ACTG (AIDS Clinical Trials Group), operated by the National Institute on Allergy and Infectious Diseases, is among the largest clinical research networks in the country. And yet, AIDS drugs remain among the most expensive drugs on the market.

The AIDS epidemic also has prompted dramatic reforms of the drug approval process, and has witnessed unlikely collaborations between consumers and industry. For AIDS drugs, the FDA has significantly streamlined its review process, cutting years off the time required for a drug to come to market, and has implemented innovative conditional approval mechanisms that permit companies to market drugs following only preliminary proof of efficacy. And yet, AIDS drugs remain among the most expensive drugs on the market.

With AIDS, the industry has again demonstrated that a "protected free market" system will offer only high prices and high profits, no matter the cost in human suffering. As a nation, it is time that we ask whether we can any longer afford the status quo. It is time that we call upon the industry to explain how research and development costs could possibly be so high. It is time to wonder, again, whether we can afford to subsidize a worldwide marketplace with record-setting prices?

Mr. Chairman, as has become increasingly clear with our healthcare delivery system in general, it is time that pharmaceutical prices in the United States are intelligently restrained, as they are in almost every other developed country in the world. We believe that this is an appropriate role for the federal government to perform, and urge that such a regulatory function be incorporated within whatever healthcare financing package the Congress ultimately adopts. Certainly, a price review board on the Canadian model would be well worth exploring.

Further, we would oppose imposing such a role on either the NIH or the FDA. These agencies have historically, and appropriately, avoided questions concerning healthcare financing. The regulation of research, safety, and economics must remain distinct. Finally, it is imperative that with respect to price regulation, the marketplace be treated as a whole. The regulation of only certain segments of the market, whether orphan drugs or CRADA drugs, no matter how compelling, must be avoided. Such a move would only further distort the market, and would serve as a disincentive for manufacturers to participate in these worthwhile programs.

Mr. Chairman, I must commend you and your staff for your tenacity with respect to this issue. Clearly, our healthcare system is at a crossroads. Prescription drugs are a vital component of that system, and I urge you, as you continue to examine the issue further, to press for the inclusion of prescription drug pricing regulation in our final healthcare reform package. Mr. Chairman, thank you again for the opportunity to testify.

The CHAIRMAN. Mr. Hodel, thank you. We will have some questions in just a moment.

Mr. Nader, we welcome you to the Committee.

STATEMENT OF RALPH NADER, CONSUMER ADVOCATE, CENTER FOR THE STUDY OF RESPONSIVE LAW, ACCOMPANIED BY JAMES LOVE, CONSUMER ADVOCATE, CENTER FOR THE STUDY OF RESPONSIVE LAW

Mr. NADER. Thank you very much, Mr. Chairman.

Again, you are to be commended for your often lonely stand on this issue over the years and the work of your committee.

Our Taxpayer Assets Group has been researching for 2 years subjects relating to the mismanagement or giveaway dimensions to taxpayer assets known as drug research and development, under the auspices of the National Institutes of Health, which has displayed an excessive modesty over the years in terms of its role.

According to the NIH's own figures, the Federal Government funds 42 percent of all national expenditures on health care research, 42 percent compared to 47 percent from private industry. The Federal Government's role in the development of new drugs spans a wide range of activities encompassing nearly all aspects of drug development, such as the discovery of new therapeutic agents, clinical testing of drugs in humans, and the development and refinement of manufacturing techniques.

The notable exception concerns the final step of drug development, which is the request for a new drug application before the FDA required before the drug can be commercially marketed. Federal support for the development of new drugs is focused on those drugs which represent the greatest gains in therapeutic value which are used to treat the most serious illnesses.

While the FDA approves hundreds of drugs for marketing every year, the number of new or important drugs is relatively small. In 1991, the FDA approved 327 new and generic drugs and biologic products. Thirty of the approvals were for new molecular entities, known as NME's, that is, drugs that are distinctly different in structure from those already on the market.

Only five of these drugs received an FDA efficacy rating of A, which is reserved for drugs which afford significant therapeutic gain. Nine of these new molecular entities received an FDA classification of E, which is reserved for drugs that treat severely debilitating or life-threatening illness, including four of the five of Class A drugs. Two drugs received FDA Class AA priority status for the treatment of AIDS.

All five 1991 FDA Class A drugs were developed with Federal funds. Six out of nine 1991 FDA Class E drugs were developed with Federal funds. Both 1991 FDA Class AA drugs for AIDS were developed with taxpayer funds. For the group, seven of the 10—1991 FDA priority drugs—Class A, E, of AA, were developed with Federal funds.

Among these priority drugs approved in 1991, those that were developed with Federal funding were priced in the marketplace considerably higher than those developed without Federal funding. Indeed, there have been 37 new cancer drugs developed, discovered, and approved for marketing since the National Cancer

Institutes's new drugs program began in 1955. Of the 37 drugs, Mr. Chairman, of the 37 cancer drugs, 34 were developed with taxpayer funding.

Mr. Love has a few brief comments.

The CHAIRMAN. Mr. Love.

Mr. LOVE. Thank you very much.

I just wanted to touch on two points very briefly. The first point is a follow-up to the comments by Representative Wyden, who has been investigating the Taxol pricing.

I have on the wall over there Table 4 from our testimony, which is a list of drugs which are used for pricing Taxol. I want to just point out very briefly some of the flaws in the methodology. This is, in fact, NCI's fair pricing methodology. They gave Bristol-Myers a list of 15 drugs, and they said, "Price it no higher than the median drug."

The list not only was arbitrary, as was pointed out by Representative Wyden, but if you take the lowest priced drug on that list, it is Levamisol, a drug which costs $100 per month, according to the National Cancer Institute, which was described to me by one of the officials at the National Cancer Institute as a bargain. In fact, that price is overpriced.

So if the lowest priced drug on the list of 15 drugs is overpriced, it is hard to imagine how you can choose the median as a fair price.

The other thing about Taxol that needs to be pointed out is that the contractor for the NIH to produce Taxol for clinical trials is now the contractor for Bristol-Myers Squibb. They are under contract, according to Security and Exchange Commission documents, to produce more than 400 kilos of Taxol for $100 million for Bristol-Myers, which has a wholesale value of $1.948 billion according to the price announced by Bristol-Myers. The contractor who is doing the manufacturing of this substance is getting $100 million. That is the indication of the result of the fair pricing methodology described there.

The last point, and it is very brief, is that if you look at the pie chart over there, which is in our testimony as one of our charts, this is the industry's estimate of how the cost of the R&D process for drugs is broken down. If you look at the Phase III part, which is where many companies get involved with drugs that are developed by the Government, about 88 percent of the cost of development of the drug has already been paid for, by the industry's own estimate.

The industry estimates that two-thirds of the cost of developing the drug comes in the pre-clinical stage. So if the Government plays a significant role in the early stages and passes the drug off to the industry in Phase 2 or Phase 3, you cannot expect them to price a drug as if they developed it from scratch as a green-field development.

Thank you very much.

[The prepared statements of Mr. Nader and Mr. Love follow:]

PREPARED STATEMENT OF

RALPH NADER

AND JAMES LOVE

CENTER FOR STUDY OF RESPONSIVE LAW

before the
Special Committee on the Aging

of the
United States Senate

on

FEDERALLY FUNDED PHARMACEUTICAL INVENTIONS

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Introduction[1]

Mr. Chairman and members of the Committee, thank you for the opportunity to testify today. Your leadership on the issue of drug pricing is richly appreciated by the millions of American consumers who pay for drugs as consumers, as purchasers of health insurance, and as taxpayers.

Over the past two years the Center for Study of Responsive Law has undertaken a review of federal policies and practices regarding the transfer of federally funded medical Research and Development (R&D) to the private sector.[2] Our initial research involved a number of detailed case studies of particular drugs, which identified numerous problems with federal policies and laws regarding the commercialization of federally funded drug R&D. More recently, we have expanded our research efforts to address the following questions:

1. What is the extent of the federal government's role in the funding of new drug development?

2. Do federal laws and policies regarding the allocation of property rights from federally funded drug R&D protect the public interest?

3. What changes in federal laws and policies are needed to ensure that drugs developed with federal funds are priced fairly?

4. What new analytical and management approaches are needed to control prices of drugs developed with federal funds?

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[1]Michael Ward of the Taxpayer Assets Project contributed to these prepared comments.

[2]On July 29, 1991 the Center for Study of Responsive Law's Taxpayer Assets Project presented testimony on the National Cancer Institute's Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb for the development of Taxol, to the House Subcommittee on Regulation, Business Opportunities, and Energy. This testimony included a discussion of the Federal Orphan Drug Act, as well as discussions of other federally funds drugs such as AZT and cisplatin. On January 21, 1992 the Taxpayer Assets Project presented comments to the Senate Subcommittee on Antitrust, Monopolies, and Business Rights on the Orphan Drug Act and government sponsored monopolies for marketing pharmaceutical drugs. On March 3, 1992 the Taxpayer Assets Project submitted comments on the Proposed Amendments to the Orphan Drug Act to the Senate Committee on Labor and Human Resources. On January 25, 1993 the Taxpayer Assets Project presented testimony to the House Subcommittee on Regulation, Business Opportunities and Energy on private sector pricing of Taxol and other pharmaceutical inventions developed with federal funding.

Summary of Comments

Our comments today will address the following points.

- According to the National Institutes of Health, the federal government funds 42 percent of all national expenditures on health care research, compared to 47 percent from private industry.

- The federal government's role in the development of new drugs spans a wide range of activities, encompassing nearly all aspects of drug development, such as the discovery of new therapeutic agents, clinical testing of drugs in humans, and the development and refinement of manufacturing techniques. The notable exception concerns the final step of drug development, which is the request for an FDA New Drug Application (NDA), which is required before the drug can be commercially marketed.

- The federal government plays a particularly important role in the highest risk research projects, including basic research, where commercial payoffs are least certain.

- In the area of federal expenditures on human use clinical trials, a relatively advanced area for drug research, the National Institutes of Health (NIH) will spend an estimated $868.8 million in fiscal year 1993, a 75 percent increase over NIH's 1989 expenditures of $495.5 million. By comparison, the members of the Pharmaceutical Manufactures Association (PMA) reported spending $1,555 million in clinical trials in 1989 (the most recent year for which data are available).

- Federal support for the development of new drugs is focused on those drugs which represent the greatest gains in therapeutic value or which are used to treat the most serious illnesses.

- While the FDA approves hundreds of drugs for marketing every year, the number of new or important drugs is relatively small. In 1991 the FDA approved 327 new and generic drugs and biologic products. Thirty of the approvals were for new molecular entities (NMEs) -- drugs distinctly different in structure from those already on the market. Only five of these drugs received an FDA efficacy rating of A, which is reserved for drugs which afford "significant therapeutic gain." Nine of the NMEs received an FDA classification of E, which is reserved for drugs that treat "severely debilitating or life threatening illness," including four of the five Class A drugs. Two drugs received FDA Class AA priority status for the treatment of AIDS.

    - All five 1991 FDA Class A drugs were developed with federal funds.

    - Six of the nine 1991 FDA Class E drugs were developed with federal funds.

    - Both 1991 FDA Class AA drugs for AIDS were developed with federal funds.

- For the group, seven of the ten 1991 FDA NME priority drugs (Class A,E or AA), were developed with federal funds.

- Among the FDA NME priority drugs approved in 1991, those that were developed with federal funding were priced considerably higher than those developed without federal funding.

  - Drugs developed without federal funding were priced at $321 to $2,376 (based upon a full year or completed course of treatment, whichever was less).

  - Drugs developed with federal funding were priced at $368 to $546,000 (based upon a full year or completed course of treatment, whichever was less).

  - Among the seven priority drugs developed with federal funding, five were priced at more than $7,000 and only one was priced less than $1,000.

- The federal government has played an enormous role in the development of new cancer drugs. There have been 37 new cancer drugs discovered and approved for marketing since the National Cancer Institute's new drug program began in 1955.[3] Of the 37 cancer drugs, 34 were developed with federal funding.

  One firm, Bristol-Myers Squibb, has benefitted the most from the NCI new drug program. Of the 34 cancer drugs developed with federal funding, 11 are marketed by Bristol-Myers Squibb, including the recent blockbuster drug Taxol.

- In comparing the relative contributions of the government and the private sector in the development of new drugs, it is important to recognize ways that industry spokesman manipulate the data. For example, studies of the industry's costs of developing new drugs typically adjust nominal expenditures for inflation, risk and the opportunity cost of capital. In contrast, the government's costs of drug development are frequently presented in nominal terms, without any adjustments for inflation, risk or the opportunity cost of capital. As a result, many observers have a grossly distorted view of the economic value of the government's drug research investments. For example, some studies report industry Phase I investments at 11 times the initial nominal cash outlays, while government agencies often report drug development costs that only reflect nominal cash outlays to contractors, and ignore the government's costs of intramural research.

- While there is ample evidence that private sector prices for drugs are excessive, there is very little data available to the government to determine fair prices. It is easier to

[3]Sixteen cancer drugs that received FDA marketing approval were discovered before the NCI new drug program began.

determine what is unfair than what is fair. In order to determine fair prices, the government needs better economic data on the pharmaceutical industry, including the costs and risks of development, manufacturing and marketing drugs, and it also needs to develop better methodologies for determining fair prices.

The recent attempt by NCI to determine a fair price for Taxol illustrates the primitive nature of NIH efforts in this regard. Taxol was discovered, manufactured and tested in humans by the National Cancer Institute. NCI gave Bristol-Myers Squibb (BMS) a Cooperative Research and Development Agreement (CRADA) that assigned to the firm the exclusive rights to commercialize all NCI past and future Taxol research. BMS, the NCI's favorite partner in drug development, paid nothing for the CRADA and will pay the government no royalties on its Taxol sales. However, BMS did agree to a "fair pricing" clause in the Taxol CRADA.

BMS's only contribution to the NDA approval for Taxol was to supply NCI with approximately 17 kilos of Taxol, and to process the paperwork for the NDA. When the NDA was approved in December 1992, BMS announced a price of $4.87 per milligram. The cost of a completed Taxol treatment will exceed $10,000 for some patients.

The Taxol price was the product of bizarre negotiations between NCI and BMS. NCI claimed that BMS simply refused to disclose any information on its development, research or marketing costs. NCI then gave BMS a list of the monthly wholesale prices for 15 arbitrarily chosen drugs and told BMS to price Taxol below the median for the group.

To consider the adequacy of the NIH's "fair pricing" methodology, consider the following facts. NCI was able to produce Taxol in small research quantities at $.60 per milligram prior to its 1989 agreement with BMS, using the same third party contractor as is used by BMS. According to the BMS contractor's recent filings with the Securities and Exchange Commission (SEC), it is under contract to produce approximately 400 kilograms of Taxol for BMS by August 1994, for which the firm expects to be paid $100 million. The wholesale value of 400 kilograms of Taxol, on the other hand, is $1.948 billion.

Since BMS is able to manufacture Taxol for about $.25 per milligram -- about 5 percent of the current wholesale price, the company's cost of providing 17 kilograms of Taxol to NCI for research purposes (which BMS owns the rights to) was less than $5 million.

In the face of criticism of the Taxol price from Representative Ron Wyden and the Taxpayer Assets Project, BMS claimed that it had made "huge" investments in the development of Taxol, which were in excessive $114 million. However, while the company refused to provide any accounting of where these "huge" expenditures had

gone, the $114 million figure clearly was based upon BMS long term contracts to supply Taxol for manufacturing purpose, and not for the research costs of the drug, which were largely borne by taxpayers. Moreover, NCI's claim that it was denied access to the BMS data reflects its contempt for its responsibilities to determine fair consumer prices for government funded drugs. The fact that BMS refused to provide financial data to NCI was a regrettable but hardly unsurmountable obstacle. While NCI is not run by rocket scientists, a child with a fourth grade education and a pencil and paper could have easily estimated BMS's development and manufacturing costs from a review of publicly available SEC documents.

Federally Funded Health Care R&D

Health care R&D is the second largest element of federally funded R&D -- only defense R&D ranks higher. The Bush Administration's fiscal year 1993 budget included more than $12 billion for health care R&D. About 70 percent of all federal health care R&D expenditures are funded through the National Institutes of Health. The remaining expenditures are funded through other agencies in the Department of Health and Human Services (HHS), as well as in the Departments of Defense, Energy, Veterans Affairs, the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), and other federal agencies.

The federal share of all national health R&D expenditures is estimated to be about 42 percent, compared to 47 percent for private industry. The remaining 10 percent is funded by non-profit foundations and other sources. (see figure 1).

The federal government's role in the development of new drugs spans a wide range of activities, encompassing nearly all aspects of drug development, such as the discovery of new therapeutic agents, clinical testing of drugs in humans, and the development and refinement of manufacturing techniques. The notable exception concerns the final step of drug development, which is the request for an FDA New Drug Application (NDA), which is required before the drug can be commercially marketed.

Investments in Clinical Trials

Among the more interesting figures are the federal expenditures on human use clinical trials, a relatively advanced area for drug research. From fiscal year 1989 to 1993 NIH expenditures on clinical trials grew from $495.5 million to $869 million, an increase of 75 percent. By comparison, the members of the Pharmaceutical Manufactures Association (PMA) reported spending $1,555 on clinical trials in 1989 (the most recent year for which data are available). (see Table 2).

Other federal agencies, ranging from ADAMHA to the Department of Defense also finance

clinical trials of pharmaceutical products.

1991 PRIORITY NEW DRUG APPROVALS

The Taxpayer Assets Project is currently examining the role of the federal government in funding the development of therapeutically important new drugs. This study will eventually cover all FDA priority new drug approvals from 1989 to 1992. Based upon our preliminary results from 1991, we conclude that the federal government's contributions to the development of new drugs is more important than is commonly believed, and is particularly important for drugs that represent the best advances in therapeutic value, or which treat the most serious illnesses.

In 1991 the Food and Drug Administration (FDA) gave marketing approval to 327 new and generic drugs and biologic products. Of this total, the majority were for variations on existing drugs or generic forms of existing compounds. Thirty of the approvals were for New Molecular Entities (NMEs), which are defined by the FDA as drugs distinctly different in structure from those already on the market.[4]

The FDA's priority review system determines the order in which pharmaceutical products will be examined for marketing approval. The first system of classification concerns the efficacy of the drug, since, for example, there is no need to rush an antibiotic through the FDA approval system if it has the same therapeutic effect as penicillin. Until 1992 drugs were classified by the FDA as either A, B or C -- according to the drug's therapeutic gain over other drugs already on the market.[5]

Class A - Drug offering significant therapeutic gain

Class B - Drug offering moderate therapeutic gain

Class C - Drug offering little or no therapeutic gain

The FDA also gave two additional priority classifications for drugs used to treat particular ailments.

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[4]Since 1980 the number of FDA NME approvals has ranged from 12 to 30, with an average of 22.5.

[5]In 1992 the FDA bowed to industry pressures to replace the A,B,C efficacy ratings with a two tiered rating of S for standard review and P for priority review. Under the FDA's new system, any drug which offers any gain in therapeutic value will receive a priority rating. This is a change from the older system, which differentiated between some gain and significant gain.

Class E - Drugs for the treatment of a severely debilitating or fatal disease

Class AA - Highest priority classification for AIDS Drugs

The efficacy ratings may be combined with the E or AA ratings. Videx, for example, is a Class A,AA,E drug, indicating that it is an important therapeutic gain over other drugs on the market that is used in the treatment of a severely debilitating or fatal disease associated with AIDS.

Our study of federal funding of new drug development focused on the 1991 FDA NME approvals that received FDA Class A, AA or E ratings. These included five Class A drugs, nine Class E drugs, and two Class AA drugs. The combined number of priority drugs was ten. Brief background information about the drugs is given in Appendix A. including are the trade and generic names, the indication for which the drug is used, the FDA efficacy and priority classification, a discussion of the federal government's role, if any, in the drug's development, and the price of the drug (which is normalized as the wholesale cost of a completed course of treatment or one year of treatment, whichever is less). When possible, a single price for an average treatment was used. In four cases it was necessary to estimate ranges of prices based upon different treatment regimes. These data are summarized in Table 2. (see also figure 2).

Although we expected the government's role to be more pronounced among the priority new drug approvals, we were surprised at the strength of the results.

All five 1991 FDA Class A drugs were developed with federal funds.

Six of the nine 1991 FDA Class E drugs were developed with federal funds.

Both 1991 FDA Class AA drugs for AIDS were developed with federal funds.

For the group, seven of the ten 1991 FDA NME priority drugs (Class A,E or AA), were developed with federal funds.

There were a number of other surprises as well. Among the FDA NME priority drugs approved in 1991, those that were developed with federal funding were priced considerably higher than those developed without federal funding. Drugs developed without federal funding were priced at $321 to $2,376, while drugs developed with federal funding were priced at $368 to $546,000. Among the seven priority drugs developed with federal funding, four were priced at $9,350 or more -- nearly four times as high as the most expensive drug developed without federal funding -- and only one was priced less than $1,000.

As expected, the federal government's Orphan Drug Act is an important factor. Six of the priority drugs, including four of the five Class A drugs benefitted from the exclusive marketing protections of the Orphan Drug Act. Moreover, four of the five highest priced

drugs received Orphan Drug marketing protection.

FEDERAL FUNDING OF NEW CANCER DRUGS

The Taxpayer Assets Project is also able to report on the federal government's role in the development of the 37 cancer drugs which have been developed since the beginning of the National Cancer Institute's new drug program in 1955. This analysis is based upon information provided by the National Cancer Institute.

In the April 1989 issue of the *International Journal of Radiation Oncology, Biology and Physics*, Bruce Chabner and Dale Shoemaker from NCI's Division of Cancer Treatment examined 37 cancer drugs. Based upon the publication dates of research, they concluded that 16 of the drugs were discovered prior to the beginning of the NCI's new drug program, while 21 of the drugs were developed afterwards. Chabner and Shoemaker identified the institution that discovered the antitumor agent, as well as NCI's contribution to the drug's preclinical and clinical research. Dr. Shoemaker and Dr. Saul Shepartz from NCI have recently provided unpublished updated information on 16 cancer drugs which were approved for marketing after the 1989 article was written. The results are reported in Table 3.

Of the 37 cancer drugs developed since 1955, the federal government was directly or significantly involved in the preclinical development of 18, and played some role the preclinical research for 10 others. In only 9 cases was NCI not involved at all in the preclinical research. When the drugs reached the stage for clinical research, NCI's role was even more pronounced. NCI played an important role in the funding of clinical research for 34 of the 37 drugs, or 92 percent of the entire group. (see figure 3).

Bristol-Myers Squibb benefitted greatly from the NCI's new drug program. Among the 34 drugs which received NCI funding, 11 are marketed by Bristol-Myers Squibb. No other drug company sells more than two cancer drugs which were developed with NCI funds. (see figure 4). Moreover, NCI played a decisive role in the preclinical research for seven of the 11 Bristol-Myers Squibb drugs, and providing significant role in the clinical research on all 11 drugs. (see figure 5).

Financial Disclosure

In order to control drug prices in an intelligent manner, the government needs better economic data on the costs and risks of development, manufacturing and marketing drugs.

The financial disclosure should identify the revenues the firm receives for the sale of the drug and the costs the firm incurs in developing, manufacturing and marketing the drug. Moreover, it is important that the firm provide historical data which shows when research and development expenses were incurred, relative to such important benchmarks, such as the beginning of Phase I, II, or III trails, the award of Orphan Drug or Patent protection, or other

events which will help evaluate the risks the firm undertook in the development of the drug.

The historical information will be important to determine how much of the industry's expenditures on the development of a drug occur at the riskiest phases. Investment before clinical trials is a higher risk than investment after clinical trials. Investments in Phase I trials are more risky than investments in Phase II trails. Investments after an FDA NDA approval are quite different than investments before an NDA approval. Research before a patent is more risky than research after a patent. If consumers or policy makers want to sort out the industry's claims about the risks involved in the development of drugs, it needs detailed information about the amounts and timing of investments, juxtaposed by the relevant milestones.

Congress should also require this disclosure to be made as public as possible. Under most most NIH CRADAs the government promises to hold the company's financial data confidential. PHS often refuses to disclose even the terms of royalty agreements, let alone company financial data.

Financial disclosures should be as widely available as possible. The information is needed for policy research, and it is also needed to evaluate the performance of government officials who work for the taxpayers.

The drug industry vastly overstates its proprietary interests in financial data. In many cases the data are only secret from the public. Firms that purchase industry trade journals or which subscribe to expensive industry surveys such as those provided by IMS on drug revenues, can easily obtain good economic data on competitors. Companies themselves regularly publish detailed information about drug revenues in their own annual reports and SEC filings. If investors can receive this information, why not provide it to a broader public in a systematic and useful format. Moreover, in many cases the firms are protected against competition by patents or other government monopolies, such as the Orphan Drug or the exclusive agreements that were used for Taxol.

Secrecy about the economics of pharmaceutical drugs is necessary to protect the industry's political interests, rather than their business interests.

Drug Pricing Models

The development of new drugs is a complicated process that involves risks and judgments. Prices that are set *ex post* should reflect these considerations, and should not create inefficient *ex ante* incentives. Policy makers need to be sensitive to the stages where price competition is possible, such as when a Phase III drug is licensed to the private sector, as well as cases where price competition is impossible, such as when a private firm already holds a patent of an agent that is the subject of government research.

We are currently working with Professor David Genesove, a member of the economics faculty at the Massachusetts Institute of Technology, and other experts on the development of models that can be used by the federal government to:

a) determine if an exclusive agreement is in the public interest;

b) increase price competition in negotiations on exclusive agreements; and

c) determine reasonable prices for drugs developed with mixed funding.

Preliminary findings from this research are expected in April.

The Taxol Fair Pricing Negotiations

The recent attempt by NCI to determine a fair price for Taxol illustrates the primitive nature of NIH efforts to control prices for government funded drugs. Taxol was discovered, manufactured and tested in humans by the National Cancer Institute. NCI gave Bristol-Myers Squibb (BMS) a Cooperative Research and Development Agreement (CRADA) that assigned to the firm the exclusive rights to commercialize all NCI past and future Taxol research. BMS, NCI's favorite partner in drug development, paid nothing for the CRADA and will pay the government no royalties on its Taxol sales. However, BMS did agree to a "fair pricing" clause in the Taxol CRADA.

BMS's only contribution to the NDA approval for Taxol was to supply NCI with approximately 17 kilos of Taxol, and to process the paperwork for the NDA. When the NDA was approved in December 1992, BMS announced a price of $4.87 per milligram. The cost of a completed Taxol treatment will exceed $10,000 for some patients.

The Taxol price was the product of bizarre negotiations between NCI and BMS. NCI claimed that under the Taxol CRADA, BMS was not required to disclose any information on its development, research or marketing costs. Rather than focus on BMS's actual costs, NCI officials told the firm that it expected the drug to be priced in the range of other cancer drugs. NCI submitted to BMS a list of 15 drugs and their estimated "monthly wholesale cost."[6] (see Table 4). BMS was asked to set the price so that one month of Taxol treatment would cost no more than the median price for the group. NCI was, in essence, telling BMS that it could price Taxol, a government funded drug invention, the same as other cancer drugs, regardless of where the funding came from, and regardless of how "fair" those prices were.

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[6]The list included 13 cancer drugs approved by the FDA since 1988, plus cisplatin, a drug licensed by BMS from Michigan State University in 1978, and hGH, an expensive and controversial growth hormone drug.

The median cost of the drugs on the list was $1,776. The highly arbitrary nature of the "list" is evident. There is one non-cancer drug on the list, human growth hormone (hGH) -- which is estimated to cost $2,520 per month. If a lower priced drug had been used instead, such as Ganite, Aredia or Ticlid, the median price would have been the $1,030 for carboplatin -- priced 42 percent lower than the $1,776 median obtained when hGH is included. Moreover, why did NCI choose the "monthly cost" when other comparisons, such as the cost of a completed treatment, are available, and why didn't NCI take into consideration such relevant factors as the size of the client population, or the types of intellectual property rights? No one from NCI wants to answer such questions.

Ironically, the lowest priced drug on the list, Johnson & Johnson's levamisole, is widely considered to be excessively priced, even at $100 per month, since the same drug has long been used to deworm sheep for about $.06 per pill -- a small fraction of the $6 per pill that Johnson & Johnson now charge human patients.

How did NCI's "list" compare to the actual prices set by BMS? A patient who receive eight vials per treatment cycle (a common dose), will pay $1686.92 a month for Taxol, a few dollars less than the $1,776 median cost from NCI's list.

To consider the adequacy of the NIH's "fair pricing" methodology, consider the following facts. NCI was able to produce Taxol in small research quantities at $.60 per milligram prior to its 1989 agreement with BMS, using Hauser Chemical Research, the same third party contractor that is currently used by BMS. According to a Hauser stock prospectus dated September 25, 1992, the firm was under contract to produce approximately 400 kilograms of Taxol for BMS by August 1994, for which the firm expected to be paid approximately $100 million. The wholesale value of 400 kilograms of Taxol, on the other hand, is $1.948 billion.

Since BMS is able to manufacture Taxol for about $.25 per milligram -- less than 6 percent of the current wholesale price -- the company's cost of providing 17 kilograms of Taxol to NCI for research purposes (which BMS owns the rights to) was probably less than $5 million.

In the face of criticism of the Taxol price from Representative Ron Wyden and the Taxpayer Assets Project, BMS claimed that it had made "huge" investments in the development of Taxol -- in excess of $114 million. However, while the company refused to provide any accounting of where these "huge" expenditures had gone, the $114 million figure clearly was based upon BMS long term contracts with Hauser, Weyerhaeuser[7] and others to supply Taxol for manufacturing purpose, and not for the research costs of the drug, which were largely borne by taxpayers. The fact that BMS refused to provide financial data to NCI was a regrettable but hardly unsurmountable obstacle. Since NCI officials were intimately knowledgeable about the cost of obtaining Taxol from third party sources, including BMS's

[7]Hauser's September 25, 1992 stock prospectus reported that Weyerhaeuser was under contract to grow 5 million yew plants for Taxol production.

own contractor, NCI could easily have estimated BMS's costs of supplying Taxol for the NCI sponsored clinical trials and compassionate use program, which were BMS's only real contributions to the Taxol NDA.

At some point Members of Congress need to examine the NCI/BMS relationship to better understand why this company has received so much from our government.

Table 1
NIH and PMA Expenditures on Clinical Trials
(millions of dollars)

Year	*NIH*	*PMA*
1988	487.6	1,333.4
1989	495.5	1,555.0
1990	609.7	
1991	745.2	
1992e	843.8	
1993e	868.8	

Source: NIH Budget Formulation Office and PMA's *1989-1991 Annual Survey Report.*

Table 2
Wholesale Prices of 1991 FDA NME Priority Drugs
(FDA Class A, AA, and E Drugs)

Drug	Efficacy	Priority	Orphan Status	Price
Drugs Developed With Government Funding				
Ceredase	A	A,E	yes	57,960 - 546,000
Fludara	A	A,E	yes	9,350
Foscavir	B	AA,E	no	21,214
Ganite	B	E	yes	368
Nipent	A	A,E	yes	33,600
Supprelin	A	A	yes	5,136 - 7,126
Videx	A	A,AA,E	no	1,745
Drugs Developed Without Government Funding				
Aredia	B	E	no	312 - 468
Survanta	C	E	yes	594 - 2,376
Ticlid	B	E	no	803

Notes: Unit drug prices were based upon wholesale price per unit, as reported in the *1992 Drug Topics Red Book* (Medical Economics Data: Montvale, N.J.: 1992) or from industry sources. Treatment regimes obtained from industry sources and the *1992 Physicians Desk Reference*, Edition 46, (Medical Economics Data: Montvale, N.J. 1992). In all cases we have reported the costs of a completed course of treatment or a year of treatment, whichever was less. FDA efficacy and priority ratings are given the "Drugs Approved in 1991," *FDA Talk Paper*, January 15, 1992.

Table 3
NCI ROLE IN THE DEVELOPMENT OF 37 CANCER DRUGS

Drug	Discovery Institution	Date of NDA	Marketing Company	NCI Preclinical Role	NCI Clincial Role
Vincristine	Lilly	1963	Lilly	none	major
Pipobroman	NCI	1966	not currently marketed	discovery	major
Hydroxyurea	NCI	1967	Squibb	discovery	major
Cytarabine	Upjohn	1969	Upjohn	significant	major
Procarbazine	Roche	1969	Hotfman-LaRoche	none	major
Mithramycin	NCI	1970	Pfizer	discovery	major
o,p-DDD	NCI	1970	Bristol	discovery	major
Bleomycin	IMC	1973	Bristol	little	major
Doxorubjcin	Farmitalia	1974	Adria	little	major
Dacarbazine	NCI	1975	Dohme	discovery	major
Lomustine	NCI	1976	Bristol	discovery	major
Carmustine	NCI	1977	Bristol	discovery	major
Cisplatin	Michigan State	1978	Bristol	significant	major
L-Asparaginase	Cornell	1978	Merck	significant	major
Daunorubicin	Farmitalia, Rhone Poulenc	1979	Ives	little	major
Streptozotocin	NCI	1982	Upjohn	discovery	major
VP-16	Sandoz	1983	Bristol	little	major
Leuprolide	Abbott	1985	Abbott	little	major
alpha-interferon	England	1986	Roche	little	major
alpha-interferon	England	1986	Schering	little	major
Mitoxantrone	NCI	1987	Lederle	discovery	major
Ifosfamide	Asta-Werke	1988	Bristol-Myers Squibb	little	major
Mitoxantrone	NCI	1988	Lederle	discovery	major
Carboplatin	NCI	1989	Bristol-Myers Squibb	significant	major
Flutamide	Schering-Plough	1989	Schering -Plough	none	none

Table 3, con't
NCI Role in the Development of 37 Cancer Drugs

Drug	Discovery Institution	Date of NDA	Marketing Company	NCI Preclinical Role	NCI Clincial Role
Zoladex	ICI	1989	ICI	none	none
BCG		1990	Connaught Organon Teknika	none	major
GM-CSF	Immunex	1990	Immunex Hoechst-Roussel	none	major
HMM	American Cyanamid	1990	US Bioscience	significant	major
Idarubicin	Farmitalia	1990	Adria Laboratories	none	none
Levamisole	Janssen	1990	Janssen	little	major
Fludarabine Phosphate	Southern Research Institute (NCI contractor)	1991	Berlex	discovery	major
G-CSF	Amgen	1991	Amgen	none	major
Pentostatin	Park-Davis (NCI contractor)	1991	Parke-Davis	significant	major
VM-26	Sandoz	1992	Bristol-Myers Squibb	little	major
IL-2	Cetus	1992	Chiron	none	major
Taxol	NCI	1992	Bristol-Myers Squibb	discovery	major

Sources: Bruce A. Chabner and Dale Shoemaker, "Drug Development for Cancer: Implications for Chemical Modifiers," *International Journal of Radiation Oncology, Biology and Physics*, April 1989, Volume 16, Number 4, pp. 907-909. Dr. Dale Shoemaker and Dr. Saul Schepartz, Division of Cancer Treatment, National Cancer Institute. Taxpayer Assets Project.

Table 4
NCI's comparison drugs for purposes of pricing Taxol

drug	*monthly wholesale price*
gm-csf	4,095
c-csf	3,010
deoxycoformycin	2,880
hGH	2,520
mitoxantrone	2,010
ifosfamids	1,960
idarubicin	1,929
bcg	**1,776**
carboplatin	1,030
fludarabine	720
cisplatin	680
hexamethylmelamine	612
zoladex	322
flutamide	216
levamisole	100
Median price	1,776
Mean price	1,591

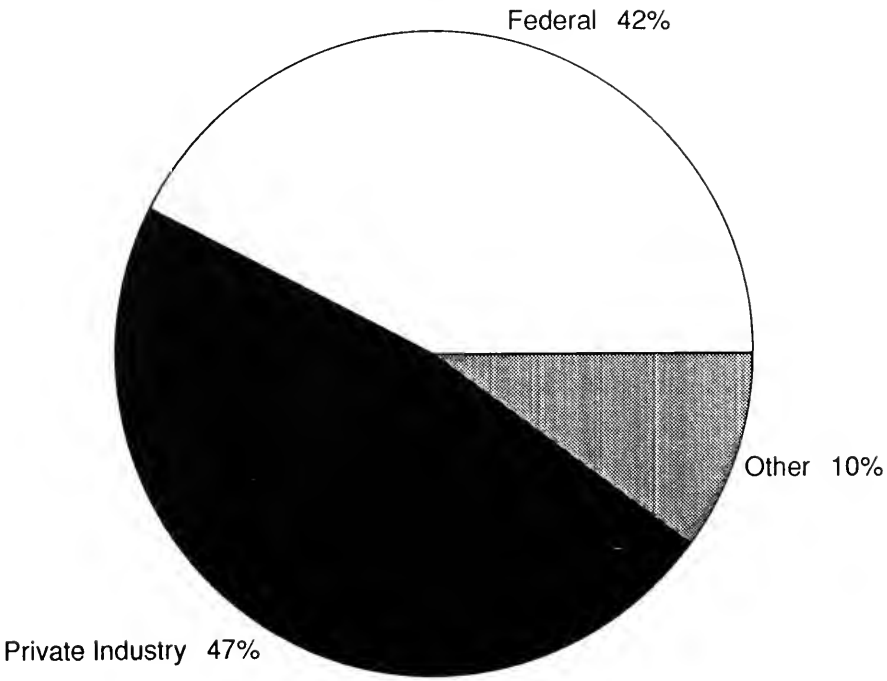
Table 5
Average Investment Lags before Drug Approval

Phase	*years from phase start to approval*	*mean phase length*
Preclinical	11.8	3.6
Phase I	8.2	1.3
Phase II	6.9	2.0
Phase III	5.0	3.0
NDA Review	2.5	2.5

Source: J.A. DiMasi et al., "Costs of innovation in pharmaceutical industry," *Journal of Health Economics* 10 (1991).

Figure 1

Sources of funding for U.S. Health Care R&D
(1990)



Source: National Institutes of Health

figure 2

1991 FDA Priority NME Drug Approvals (class A,AA or E)

Wholesale Drug Prices, Based Upon One Year or Completed Course of Treatment, Whichever is Less

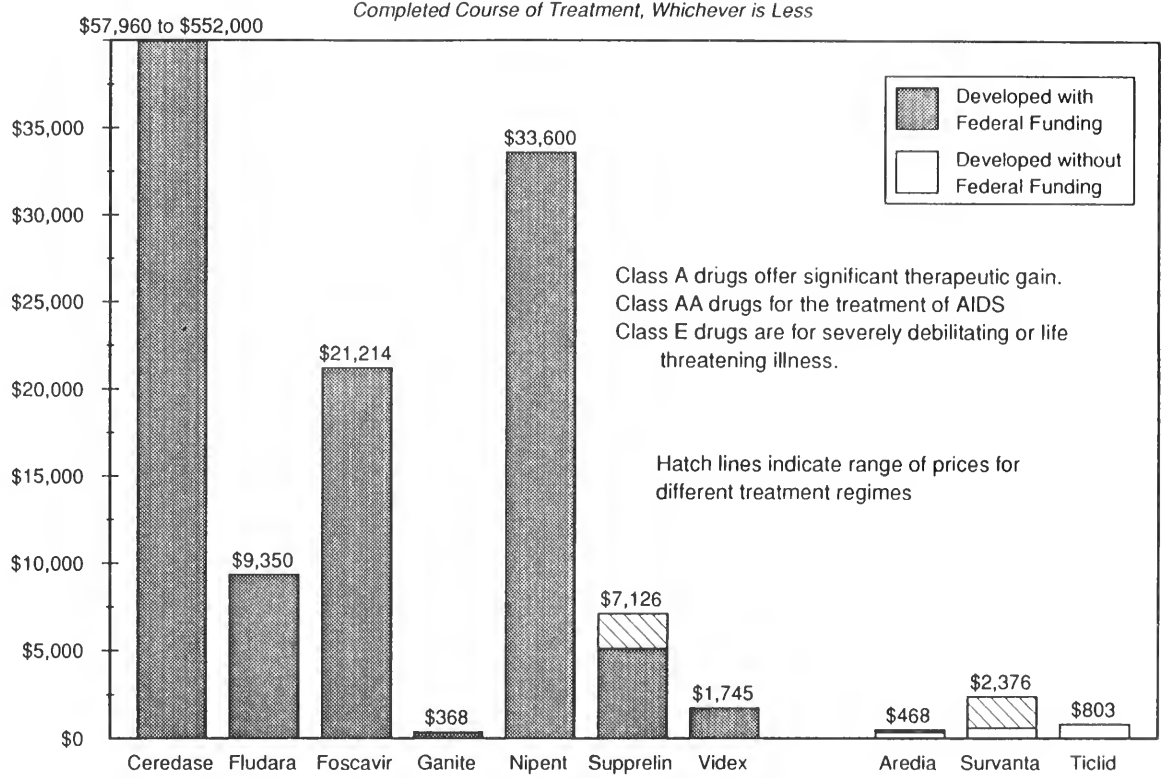
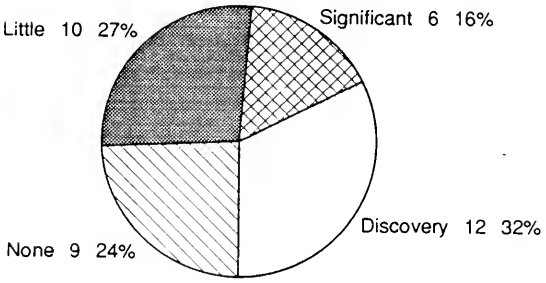
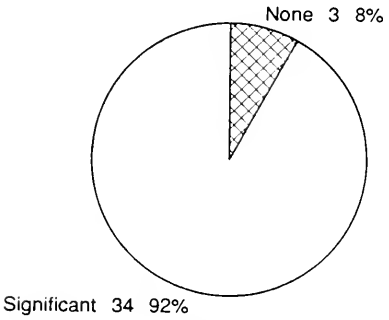


figure 3

National Cancer Institute Research Role for 37 Cancer Drugs



Preclinical Research

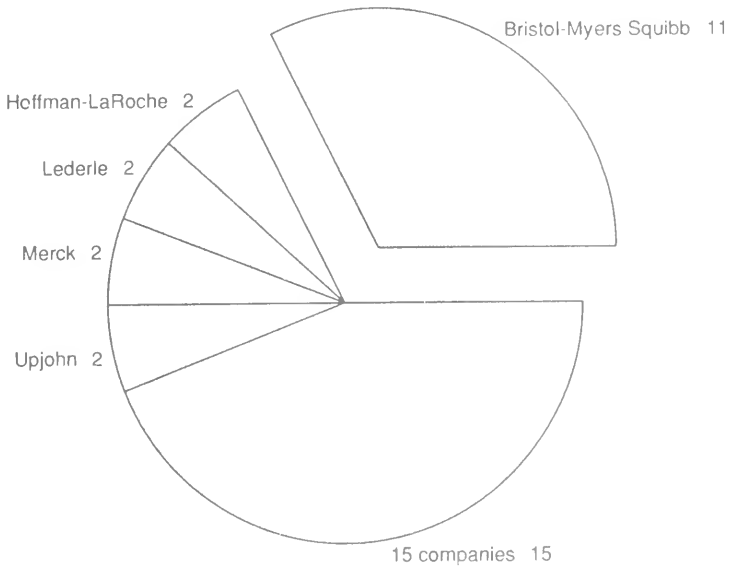


Clinical Research

Source: NCI

figure 4

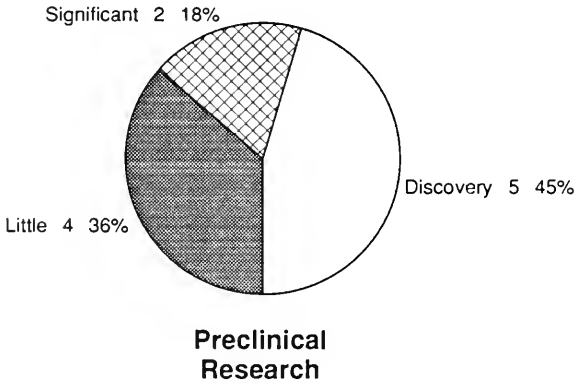
Companies that Market 34 Cancer Drugs Developed with Funding from National Cancer Institution



Source: NCI

figure 5

NCI Role in the Development of 11 Cancer Drugs Marketed by Bristol-Myers Squibb



Note: Cancer drugs developed after 1955

figure 6

Opportunity Cost of One Dollar Invested in R&D

(at date of NDA approval)

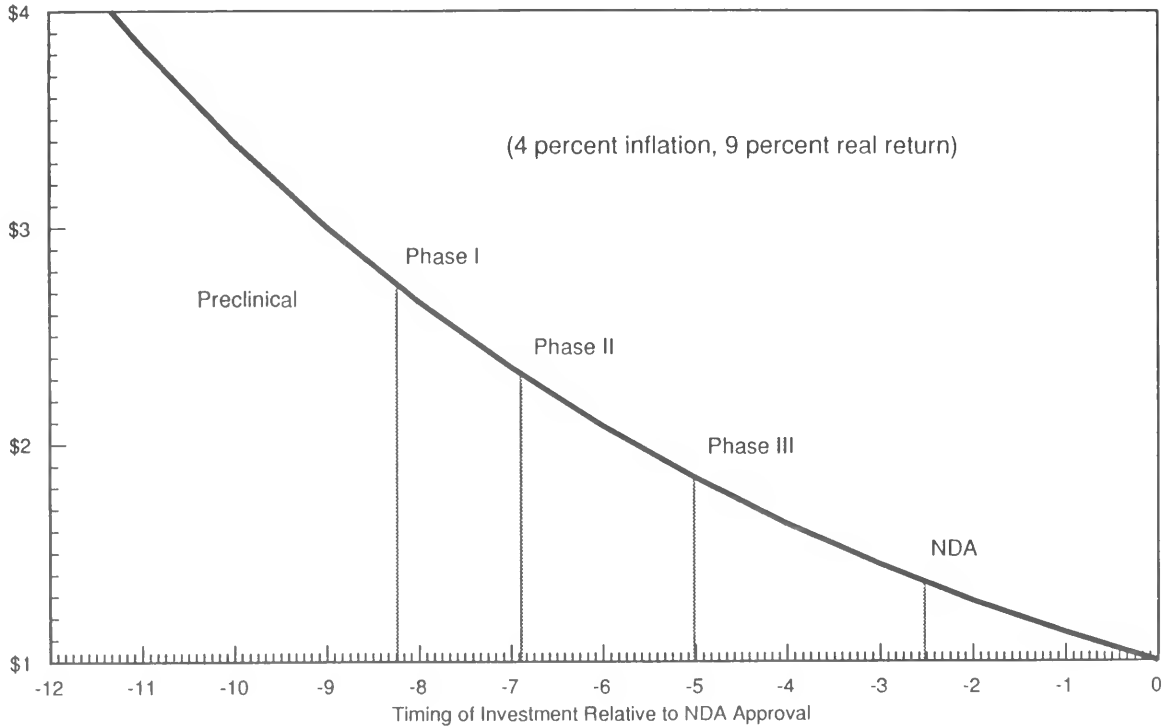


figure 7

Opportunity Cost of One Dollar Invested in R&D

(at Date of NDA Approval)

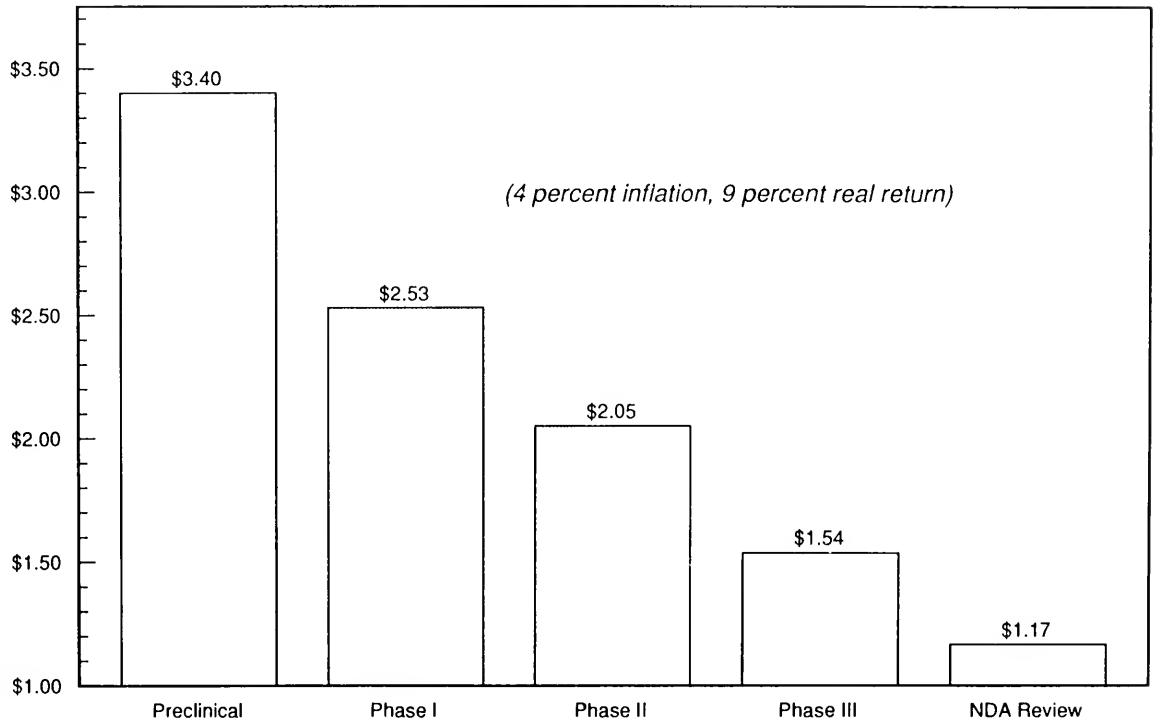


figure 8

Cost Mulitplier to Adjust for Risk

Based Upon Probability of Success

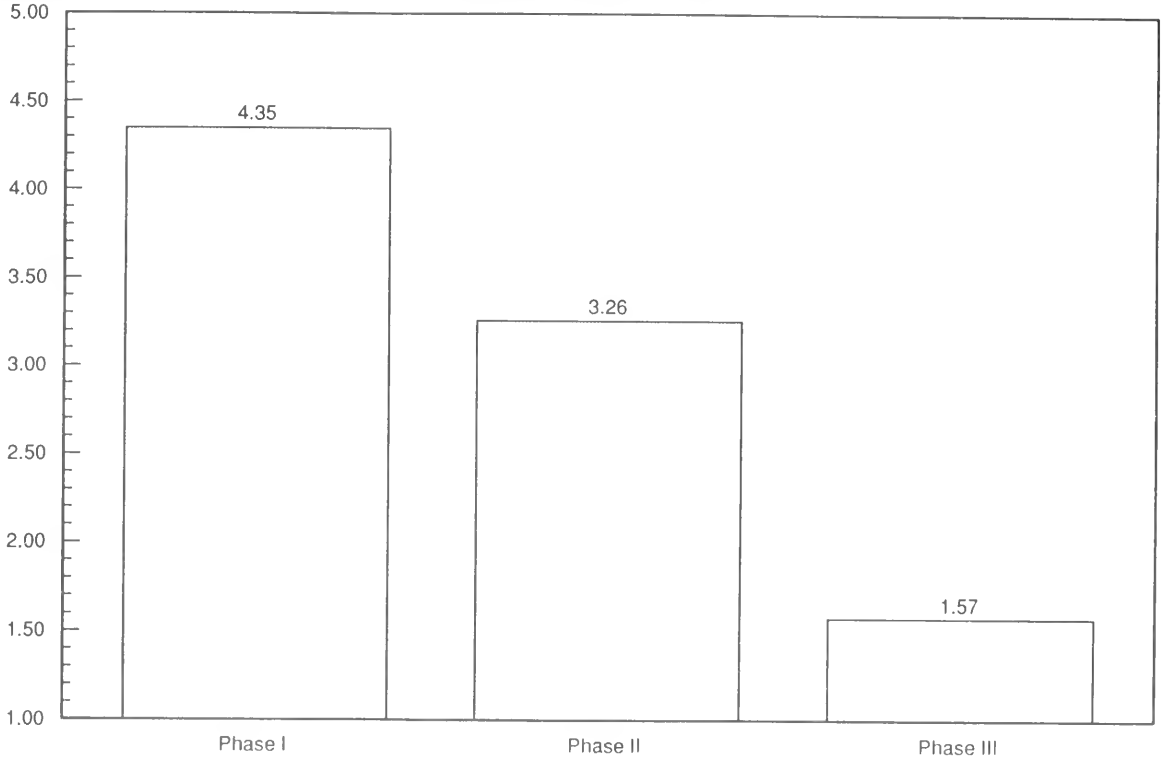


figure 9

Cost Mulitplier to Adjust for Risk and Opportunity Cost of Capital

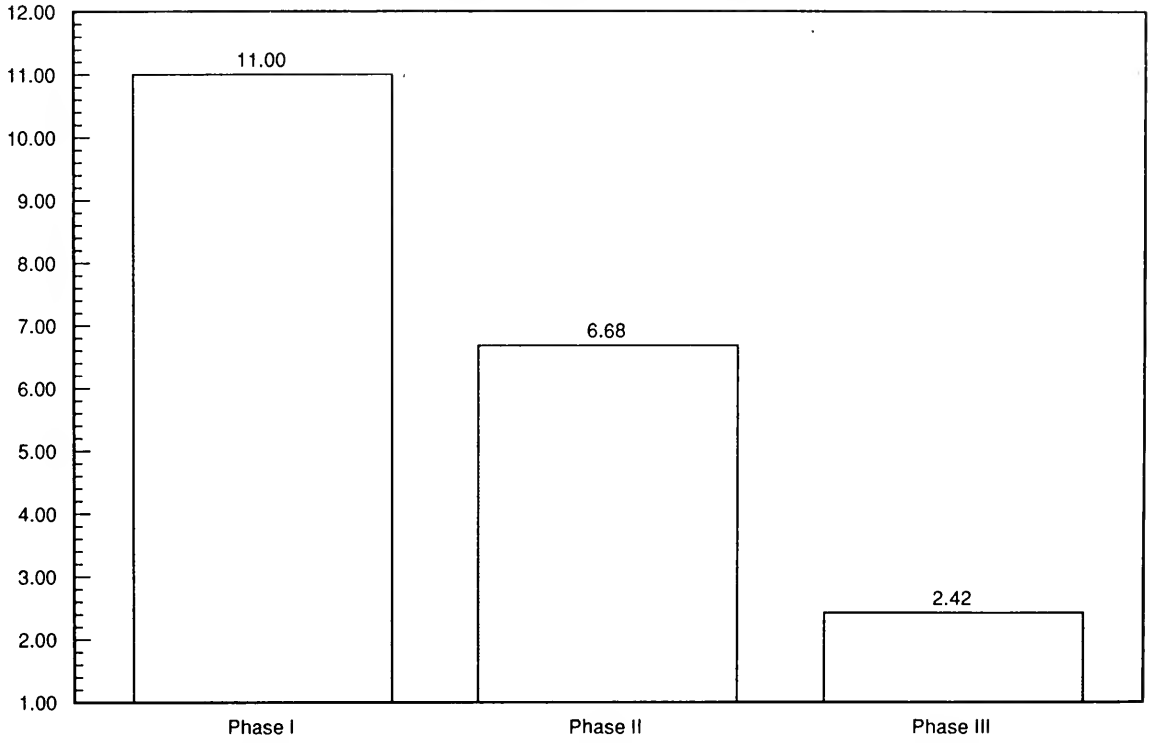
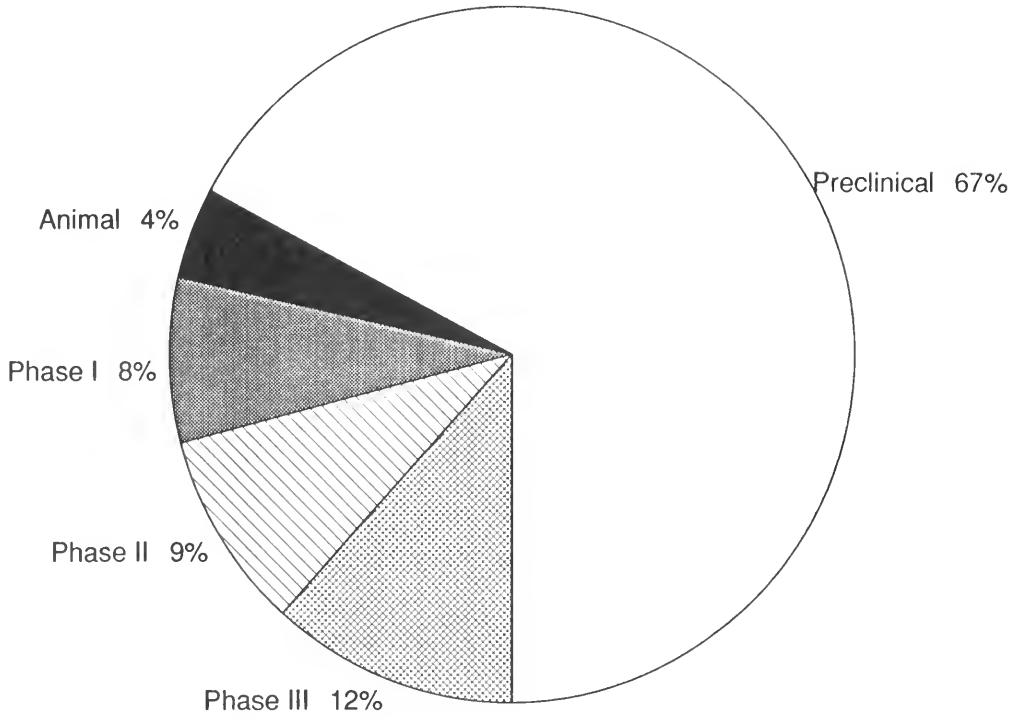


Figure 10

Estimated Shares of Drug R&D Costs



Source, DiMasi, Hansen, Grabowski and Lasagna 91

Appendix A

FEDERAL INVOLVEMENT IN TEN PRIORITY DRUGS APPROVED BY THE FDA IN 1991

Definition of Priority Drugs

In 1991 the Food and Drug Administration (FDA) gave marketing approval to 327 new and generic drugs and biologic products. Of this total, the majority were for variations on existing drugs or generic forms of existing compounds. Thirty of the approvals were for New Molecular Entities (NMEs), which are defined by the FDA as drugs distinctly different in structure from those already on the market.[1]

The FDA's priority review system determines the order in which pharmaceutical products will be examined for marketing approval. The first system of classification concerns the efficacy of the drug, since, for example, there is no need to rush an antibiotic through the FDA approval system if it has the same therapeutic effect as penicillin. Until 1992 drugs were classified either A, B or C according to the drug's therapeutic gain over other drugs already on the market.

Class A - Drug offering significant therapeutic gain

Class B - Drug offering moderate therapeutic gain

Class C - Drug offering little or no therapeutic gain

The FDA also gave two additional priority classifications for drugs used to treat particular ailments.

Class E - Drugs for the treatment of a severely debilitating or fatal disease

Class AA - Highest priority classification for AIDS Drugs

The efficacy ratings are combined with the E or AA rating. Videx, for example, was a Class A,AA,E drug, indicating that it is an important therapeutic gain over other drugs on the market that is used in the treatment of a severely debilitating or fatal disease associated with AIDS.

Our population of 1991 priority drugs includes all ten FDA NME approvals that received FDA Class A, AA or E ratings. Of these, five were Class A drugs, nine were Class E drugs, and two were Class AA drugs.

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[1]Since 1980 the number of FDA NME approvals has ranged from 12 to 30, with an average of 22.5.

Trade Name:	Aredia
Generic Name:	pamidronate disodium
Marketing company:	Ciba-Geigy
Date of FDA marketing approval:	October 31, 1991

Indication

Aredia is used to treat cancer-related hypercalcemia. This disease is a serious problem in the clinical management of patients with cancer. Almost one-half of women with metastatic breast cancer eventually develop hypercalcemia.

FDA Classification

Efficacy: B Priority: E

Orphan Drug status: no

Federal Involvement

discovery of agent:	no
pre-clinical research:	no
clinical research:	no

No federal research or funding was used in development of Aredia.

Intellectual Property Rights

Aredia was discovered by Ciba-Geigy researchers in England and subsequently patented in the U.S.

Drug Economics

Mild hypercalcemia is treated with a single 60mg infusion of Aredia costing $312. A severe case of hypercalcemia costs $468 using a single 90mg infusion.

Trade Name:	Ceredase
Generic Name:	alglucerase
Marketing Company:	Genzyme Inc.
Date of FDA marketing approval:	April 5, 1991

Indications

Ceredase is used in the treatment of Gaucher's disease, an inherited metabolic disorder effecting the production of a critical bodily enzyme. Gaucher's disease is severely debilitating disease that causes hematologic disorders, enlargement of the liver and spleen, bone erosion and pain. A significant number of Gaucher's disease victims in the U.S. are Ashkenazic Jews.

FDA Classification

Efficacy: A Priority: A,E

Orphan Drug status: yes

Federal Involvement in Development

discovery of agent:	yes
pre-clinical research:	yes
clinical research:	yes

A 1992 study, conducted by the congressional Office of Technology Assessment (OTA), described three very important breakthroughs in the treatment of Gaucher's disease. First, in the mid-1960's Dr. Roscoe Brady of the NIH isolated the glucocereborosidase enzyme that Gaucher sufferers lack. Second, during the 1970's NIH researchers discovered a method for harvesting the enzyme from the human placenta. Third, government scientists discovered a chemical modification that greatly improved the effectiveness of the enzyme. This modified form became Ceredase. In addition to this developmental research, the National Institutes of Health conducted numerous clinical trials during the 1980's.

Intellectual Property Rights

Because extensive research about alglucerase has been published, the drug is non-patentable. Genzyme has seven years of marketing exclusivity under the Orphan Drug Act.

Drug Economics

According to the Congressional Office of Technology Assessment (OTA), the treatment cost to patients, most of whom must take the drug indefinitely, ranges from $57,960 to $546,000 per year.

According to Company figures provided to OTA, the cost of producing, manufacturing, and marketing costs for Ceredase was $1.90 per unit in 1992. The unit cost of production is expected to fall with higher scale production. The wholesale price of Ceredase is $3.50 per unit, a markup of 84 percent over the 1992 production costs. OTA estimates that Genzyme spent $29.4 million on R&D for Ceredase. A significant portion of these expenditures were for the acquisition of alglucerase manufacturing facilities.

OTA estimates that 2,100 to 11,000 persons are candidates for treatment of Type 1 Gaucher Disease.

Trade Name:	Fludara
Generic Name:	fludarabine phosphate
Marketing Company:	Berlex Laboratories
Date of FDA marketing approval:	April 1991

Indications

Fludara is used in the treatment of chronic lymphocytic leukemia, an often fatal disease.

FDA Classification

Efficacy: A Priority: A,E

Orphan Drug Status: yes

Federal Involvement in Development

discovery of agent:	yes
pre-clinical research:	yes
clinical research:	yes

The Division of Cancer Treatment (DCT) at the National Cancer Institute (NCI) conducted extensive research on converting ara-A, an acute leukemia drug limited by its rapid degradation in the body into a more insoluble and useful drug. In 1982 two Department of Health and Human Service workers discovered a way to convert ara-A into a more insoluble compound, fludarabine phosphate.

After concluding preclinical toxicology and pharmokinetic studies, the DCT proceeded with clinical trials on Fludarabine in 1983. A number of clinical trials have been conducted or sponsored by DCT, NCI; 8 are currently active. There have been nine Phase I and three Phase I-II trials in adults and an additional 4 Phase I-II trials have been conducted in children. Fludara was approved on the basis of two single arm studies conducted at the Southwest Oncology Group, a branch of NCI's cooperative research group, and M.D. Anderson working under federal grants.

Intellectual Property Status

The Department of Health and Human Services received a patent for the drug in 1982. In 1984 the National Technical Information Service (NTIS) licensed the patent to Dupont Chemical Company and Triton Biosciences who later sold their rights to Berlex Laboratories the current marketer of Fludara. As a result of Orphan Drug status, Berlex enjoys exclusive marketing rights through 1998.

Drug Economics

Fludara is administered for five consecutive days. This cycle is then repeated every 28 days, or 13 times a year. The daily dose is 25mg per m^2 of body surface. A person with a body surface of $1.7m^2$ would use five vials per treatment, or 325 vials per year. The cost of one vial is $143.85. Some patients will receive the drug for the rest of their lives. The cost of a year of treatment for a person of average size is $9,350.

Trade Name:	Foscavir
Generic Name:	foscarnet sodium
Marketing Company:	Astra Pharmaceuticals
Date of FDA marketing approval:	September 27, 1991

Indication

Foscavir is used in the treatment of the cytomegalovirus, an opportunistic infection associated with HIV. It is the most prevalent eye infection and leading cause of vision loss among AIDS patients.

FDA Classification

Efficacy: B Priority: AA,E

Orphan Drug status: no

Federal Involvement

discovery of agent:	no
pre-clinical research:	no
clinical research:	yes

Of the five clinical trials evaluated for the NDA filed in June 1990, two were sponored by NIH, at a cost of $3.05 million. NIH research on Foscavair continued after Astra received FDA marketing approval. To date the U.S. government has spent an estimated $21.8 million on Foscavir clinical trials.

Intellectual Property Rights

Foscavir's patent is held by Astra Pharmaceuticals.

Drug Economics

Foscavir is administered in two stages. The induction therapy is 60mg/kg of body weight 3 times per day for 21 days. This is followed by a 90mg/kg maintenance dose that is given indefinitely. A 110 pound person would receive 1,737 grams of Foscavir over the period of one year. The wholesale price of Foscavir is $73.28 for 6 grams. The cost of 21 days of induction therapy followed by 344 days of maintenance therapy is $21,214.

Trade Name:	Ganite
Generic Name:	gallium nitrate
Marketing Company:	Fujisawa Friar
Date of FDA marketing approval:	January 17, 1991

Indications

Ganite is used in the treatment of cancer-related hypercalcemia. This disease is a serious problem in the clinical management of patients with cancer. According to some researchers, almost one-half of women with metastatic breast cancer eventually develop hypercalcemia.

FDA Classification

Efficacy: B Priority: E

Orphan Drug status: yes

Federal Involvement in Development

Discovery of agent:	yes
pre-clinical research:	yes
clinical research:	yes

Researchers at Memorial Sloan-Kettering Institute for Cancer Research in New York City discovered gallium nitrate's effectiveness in the treatment of hypercalcemia. They were working under a general research grant given to Sloan-Kettering by the National Cancer Institute. The research was conducted with gallium nitrate provided by the Division of Cancer Treatment of NCI. The clinical trials were held at Sloan-Kettering using NCI and FDA grants.

Intellectual Property Status

As a result of the research performed at Sloan-Kettering with NCI funding, Sloan-Kettering applied for and received a patent on the use of gallium nitrate to treat calcium homeostasis disorders in July of 1985. This and Orphan Drug status ensure Fujisawa Fria exclusive marketing rights.

Drug Economics

Ganite is administered at a dose of 200mg/m^2 of body surface for five days. Four 500mg vials, priced at $92 would be necessary to treat a person with a body surface of 1.7 m^2, for a total cost of $368.

Trade Name:	Nipent
Generic Name:	pentostatin
Marketing Company:	Parke-Davis
Date of FDA marketing approval:	October 15, 1991

Indication

Nipent is used in the treatment of Hairy Cell Leukemia. This chronic illness affects approximately 2500 patients in the U.S. About 500-600 new patients are diagnosed yearly. Hairy Cell Leukemia has a median survival period of approximately four years from the time of diagnosis.

FDA Classification

Efficacy: A Priority: A,E

Orphan Drug status: yes

Federal Involvement in Development

discovery of agent:	Parke-Davis with funding from NCI
pre-clinical research:	yes
clinical research:	yes

Even though Parke-Davis discovered pentostatin the National Cancer Institute was the most significant organization involved in the development. According to Dr. Saul Schepartz of NCI, the federal government played a "significant" role in the pre-clinical research of pentostatin. The approval of Nipent was based on Phase II data from 133 patients during five clinical trials, with most of the clinical work conducted at M.D. Anderson Hospital and by Cancer Leukemia Group B with NCI funding.

Intellectual Property Status

Parke-Davis applied for and received a patent for pentostatin.

Drug Economics

Nipent is administered at a dose of $4mg/m^2$ of body surface once a week for 28 weeks. The cost of one vial is $1,200. The cost of 28 weeks of treatment is $33,600.

Trade Name:	Supprelin
Generic Name:	histrelin acetate
Marketing Company:	Roberts Pharmaceuticals
Date of FDA marketing approval:	December 24, 1991

Indication

Supprelin, a synthetic agonist of the gondatropin releasing hormone (GnRH) is used in the treatment of central or unexplained precocious puberty, a condition in which young children develop secondary sexual characteristics of adolescents.

FDA Classification

Efficacy: A Priority: A

Orphan Drug status: yes

Federal Involvement

discovery of agent:	yes
pre-clinical research:	yes
clinical research:	yes

Jean Rivier of the Salk Institute, a non-profit research organization, discovered histrelin acetate while conducting government funded research on the basic mechanisms of GnRH's. The Salk Instute conducted pre-clinical toxicology and animal studies as well as producing the first batches of histrelin acetate for the earliest clinical research. Dr. William Krawley, of Massachussets General Hospital, in the midst of conducting ten years of NIH funded research on GnRH's, used histrelin acetate in the treatment of precocious puberty. This research was the largest group of data used in the NDA for histrelin acetate.

Intellectual Property Rights

Patent #4244946, issued in January 13, 1981 expires January 13, 1998.
Orphan Drug protection expires on December 24, 1998.

The Salk Institute licensed their patent for histrelin acetate to six pharmaceutical companies. All but Johnson and Johnson (J&J) gave up their license. Ortho pharmaceuticals, a subsidiary of J&J, sold its license to Robert's Pharmaceutical, the current marketer of Supprelin.

Drug Economics

Histrelin acetate is purchased in a 30 day kit that includes syringes and medicine. The two most commonly used solutions are 500 mg/ml and 1000 mg/ml costing $428 and $594, respectively. A years supply of the smaller dose costs $5,136, the larger dose costs $7,126. Since this drug retards the onset of puberty, a four year old child with precocious puberty might have to take the drug until the normal onset of puberty, 11, 12, or 13 years of age.

Trade Name:	Survanta
Generic Name:	Beractant
Marketing Company:	Ross Laboratories
Date of FDA marketing approval:	July 1, 1991

Indication

Survanta is a drug used to treat critically ill premature infants with Respiratory Distress Syndrome (RDS). RDS afflicts approximately 50,000 of the 250,000 premature infants born in the U.S. each year and kills approximately 5,000 of those infants annually.

FDA Classification

Efficacy: C Priority: E

Orphan Drug status: yes

Federal Involvement

discovery of agent:	no
pre-clinical research:	no
clinical research:	no

No federal research or money was used in the development of Survanta.

Intellectual Property Rights

The Tokyo Tanabe Co. discovered Survanta in Japan and subsequently applied for and received a patent in the U.S. Abbott Laboratories, the parent company of Ross Laboratories, licenses this drug from Tokyo Tanabe. Also, Orphan Drug status guarantees exclusive marketing rights to Ross Laboratories.

Drug Economics

Infants can receive between one and four vials of Survanta at a cost of $594 to $2,376.

Trade Name:	Ticlid
Brand Name:	ticlopidine hydrochloric acid
Marketing Company:	Syntex Laboratories
Date of FDA Marketing Approval:	

Indication

Ticlid is used for the management of thrombotic strokes, a common and often fatal affliction.

FDA Classification

Efficacy: B Priority: E

Orphan Drug status: no

Federal Involvement

discovery of agent:	no
pre-clinical research:	no
clinical research:	no

No federal research or money was used in the development of Ticlid.

Intellectual Property Status

Ticlid was discovered by Sanofi, a French pharmaceutical company. Syntex licensed Ticlid from this company and re-evaluated previous studies and conducted its own pre-clinical and clinical trials.

Drug Economics

One 250mg tablet is taken twice a day indefinitely. The wholesale cost of each tablet is $1.10. The annual cost of Ticlid therapy is $803.

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Trade Name:	Videx
Generic Name:	ddI
Marketing Company:	Bristol-Myers Squibb
Date of FDA Marketing Approval:	October 9, 1991

Indications

Videx is one of three antiviral drugs used to combat the AIDS virus.

FDA Classification

Efficacy: A Priority: A,AA,E

Orphan Drug status: approved but withdrawn by Bristol-Myers Squibb

Federal Involvement in Development

discovery of agent:	yes
pre-clinical research:	yes
clinical research:	yes

The National Cancer Institute identified the activity of ddI against HIV in the laboratory, performed preclinical development, and initiated the first clinical trials in humans. NCI estimated that its costs for developing ddI were $6.8 million through the end of 1990.

Intellectual Property Rights

In 1989 the Department of Health and Human Service received a patent for ddI. On February 1, 1988, NCI signed an exclusive license with BMS giving the company exclusive rights to market the drug for ten years following the first commercial sale.

Drug Economics

BMS estimates the average wholesale cost for a patient receiving ddI will be $1,745 per year.

Sources

At present the federal government does not publish information that routinely identifies the federal role in the development of new drugs. In order to establish what role, if any, the government played in the development of the drug, it was necessary to survey a wide range of sources. Often the pharmaceutical companies themselves down played or refused to acknowledge the government's role in the development of the drug. For example, a spokesperson for Roberts Pharmaceutical refussed to acknowledge any federal role in the development of Supprelin, while in fact, the drug was discovered at the Salk Institute and clinical testing was carried out by the Salk Institute and Massachusetts General Hospital with funding from NIH.

It is typically necessary to contact government agencies or the non-profit institutions that were directly involved in the research to identify the nature of government funded research in the development of the drug. The National Institutes of Health and its member agencies were helpful when asked specific questions, although only the Division of Cancer Treatment of the National Cancer Institute had routinely tracked its role in the development of new drugs.

In most cases it is necessary to research the history of the each drug's development through medical journals. Much of this research was assisted by the National Library of Medicine's MEDLINE database. It was also helpful to examine drug patents. The Department of Health and Human Services publishes *Approved Drug Products*, which lists all products which have been approved for marketing under Sections 505 and 507 of the Federal Food, Drug, and Cosmetic Act, including patent numbers and expiration dates. Patents were obtained from the Patent and Trademark Office (PTO). The PTO maintains an online system which can search the full text of all U.S. patents, but it does not provide public access to the system except in its reading rooms -- at a rate of $40 per hour plus $.25 per patent page. This service is also available from commerical data vendors, at very high prices. For example, the PTO estimates that a typical searcher would pay $340 per hour to search patents on LEXPAT, a service based upon the PTO's publicly funded database, which is marketed by Mead Data Central.[2]

The Research Documentation Section, Information Systems Branch, Division of Research Grants at the National Institutes of Health maintains the CRISP database, which contains data on the research programs supported by the U.S. Public Health Service from 1972 to the present. This database includes research grants, contracts, and cooperative agreements funded

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[2]The PTO's automated patent system cost an estimated $300 million to develop, and currently serves about 1,500 patent examiners. In 1991 the Taxpayer Assets Project asked that the PTO to modify its database to include specific information about the government's role in the funding of new patentable inventions. The Taxpayer Assets Project also asked that the PTO provide remote online public access to the government's system, at prices which reflect the government's incremental cost of providing access to the database. No action on either request has been taken.

by NIH and ADAMHA, selected research grants funded by the Centers for Disease Control, FDA, the Health Resources and Services Administration, and the Agency for Health Care Policy, as well as selected information on the intramural programs of NIH, ADAMHA and FDA. The CRISP database is available online from commercial vendors such as Dialog, at prices too high for us. However, NIH does respond to mailed requests for searches. While the CRISP database is a helpful source of information that should be more readily available to researchers, the data are often only suggestive. For example, for many government grants or contracts, numerous drugs are under investigation, and it is not possible to obtain specific allocation of funding for individual drugs.

Drug prices were based upon wholesale price per unit, as reported in the *1992 Drug Topics Red Book*,[3] or from industry sources, and treatment regimes obtained from industry sources and the *1992 Physicians Desk Reference*.[4] In all cases we have reported the costs of a completed course of treatment or a year of treatment, whichever was less.

Information on the revenues from drug sales and the company's costs of development, manufacturing and marketing are incomplete. Revenues from individual drugs are collected by IMS, a Philadelphia research firm, and are readily available to the drug companies themselves, but the data are licensed with substantial restrictions against redissemination and are too expensive for most non industry researchers. In several cases, company SEC filings and annual reports contain public disclosure of information on individual drug revenues and company R&D or manufacturing expenditures. While federal agencies have a wealth of information about hospital and doctor services, no federal agency has responsibility for collecting or disseminating information about the economics of the pharmaceutical industry.

[3]Published by Medical Economics Data: Montvale, N.J. 1992.

[4]Edition 46, published by Medical Economics Data: Montvale, N.J.

Appendix B

Notes on federal policies to transfer ownership of federally funded R&D

Policies concerning the allocation of intellectual property rights from federally funded research have changed markedly since World War II. There once was a broad consensus that federally funded research should be liberally shared with the public, either by allowing research to enter the public domain, or by licensing property rights, such as patents, on a non-exclusive basis. In recent years this has given way to a more proprietary approach.

Many of the important changes in federal policy occurred in the 1980's. These include the enactment of the Stevenson-Wydler Technology Innovation Act and the Bayh-Dole University and Small Business Patent Procedures Act (both passed in 1980) the 1984 mendments to the Bayh-Dole Act, and the Federal Technology Transfer Act of 1986.[5] President Reagan also issued a number of Federal Executive Orders and memorandums which broadened the rights of government contractors and grant recipients to obtain titles to federally funded research products and grant exclusive licenses for commercial development.[6]

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[5]The Stevenson-Wydler Technology Innovation Act (PL. 96-480), Oct 25, 1980, encouraged the transfer of intellectual property rights from federal research to the private sector. It also provided for cooperative research agreements and for supporting Centers for Industrial Technology affiliated with non-profit institutions, which could take title to inventions developed with federal funds.

The Bayh-Dole Act University and Small Business Patent Act (PL 96-517), Dec 12, 1980, gave small businesses and non-profit institutions title to inventions that they developed under federal grants or contracts. The Act retained a license for government use.

A 1984 law (P.L. 98-620) repealed the 5-year limitation on the use of exclusive licenses by non-profit institutions that held title to inventions that had been developed with federal funds, and allowed non-profit organization to take title to inventions when operating government owned laboratory facilities.

The Federal Technology Transfer Act (PL-99-502), Oct 20, 1986, expanded the ability of agencies and laboratories to enter into Cooperative Research and Development Agreements (CRADAs). CRADAs typically involve joint research efforts between the government and industry, where a private firm obtains a promise that it will obtain exclusive commercial rights to research data and patents that are produced by the parties.

[6]February 18, 1983, President Reagan issued a memorandum instructing federal agencies, where not prohibited by law, to grant all contractors the same right to invention titles that the Bayh-Dole Act granted to small businesses and non-profit institutions. On April 10, 1987, President Reagan issued Executive Order 12591, instructing agencies to allow laboratories to enter into CRADAs and to develop a policy allowing contractors to retain rights to software and other technical data, with a reservation of royalty-free use to the government. The order also reaffirmed the policy in his 1983 memo of waiving government title rights to contractors

These measures accomplished the following:

i. In those cases where federal research funds were managed by non-government personnel, contractors or grant recipients were given title to a wide variety of government funded research rights, with few restrictions on how these rights could be exploited.

ii. In those cases where the federal government retained title to the research products (such as research carried out by government employees or by contractors or grant recipients who were not qualified to take title to the research) federal agencies were told to place an increasing emphasis on exclusive marketing agreements with firms to commercialize the research products.

Patent, copyright, trade secret status and other measures are used to control access and ownership of government funded research. Private corporations routinely obtain exclusive marketing privileges on everything from government funded software and technical databases to inventions of new drugs.

Rationales for this more proprietary approach to federal research are varied, but two stand out, in terms of the frequency to which they are employed and the degree to which they are believed:

i. the need to provide incentives for the commercial development of a product, and

ii. the need to prevent foreign interests from benefiting from U.S. funded research and development.

While these rationales are contradictory (the need to prevent foreign companies from developing U.S. technology suggests that sufficient incentives already exist for commercial development), they are often used simultaneously as a catch-all to justify policies.

These policy guidelines, which apply to all areas of federally funded research, have received wide bipartisan support in Congress, due in no small part to aggressive lobbying and generous political contributions by companies in defense, energy, pharmaceutical, and other fields, which have benefitted from these transfers. Critics worry that universities are becoming too concerned with potential commercial rewards from research, and are abandoning important types of basic research or restricting the free flow of information among scientists. There are also concerns that the large emphasis on exclusive marketing agreements will harm consumers, or lead to anticompetitive practices, such as blocking the development of related

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wherever possible. On December 22, 1987, President Reagan issued Executive Order 13532, requiring all agencies to remove licensing restrictions on inventions made with federal assistance.

technologies, where companies which would use the government research product as an input for a different product. Others have questioned the policies on the grounds that taxpayers should receive greater benefits from its investments. For example, in a minority report on the 1980 Bayh-Dole Act, which gave small businesses and non-profit institutions title to inventions developed under federal grants or contracts, Congressman Jack Brooks said:

> The major problem I have with H.R. 6933 is that it violates a basic provision of the unwritten contract between the citizens of this country and their government; namely, that what the government acquires through the expenditure of its citizen's taxes, the government owns. Assigning automatic patent rights and exclusive licenses to companies or organizations for inventions developed at government expense is a pure giveaway of rights that properly belong to the people.
>
> . . .The federal government has the equivalent of a fiduciary responsibility to the taxpayers of the country. Property acquired with public funds should belong to the public. Deviations from that fundamental principle should be allowed only where a compelling justification can be shown and where the voice of the public can be heard in protest. This legislation stands that principle on its head by automatically conveying title or the exclusive right to use public property to private entities and placing the burden on the federal government to demonstrate that a retrieval of those rights is in the public interest.

Nowhere are these issues as important as in the medical field, where the public investment is enormous, and the product will not be a better microwave oven, but better health or even life itself. On the one hand it is important that there are proper incentives to develop new medicines and other health care technologies. On the other hand, consumers of medical technologies are uniquely vulnerable to monopoly pricing.

The Federal Orphan Drug Act is also an important mechanism for allowing private firms to obtain monopolies on government funded inventions. Since we have previously addressed this issue at length to other congressional committees, we will reference our earlier statements, and add only a few comments.[7] Today the Orphan Drug Act is primarily viewed as a mechanism to obtain seven years exclusive marketing rights (a feature that was considered unimportant when the legislation passed a decade ago). Thus, the Act is most important when company's do not hold patents for the drugs. A common reason that a drug cannot be patented is because researchers have already reported results in academic journals. This is more likely the result of research funded by the government than research funded by the industry, since the drug companies are known for exercising tight controls on a researcher's right to publish before applications for patents have been processed.

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[7]See James P. Love, "The Orphan Drug Act and Government Sponsored Monopolies for Marketing Pharmaceutical Drugs," comments submitted to the Senate Judiciary Committee's Subcommittee on Antitrust, Monopolies and Business Rights, January 21, 1992.

Because much government funded research ends up in the public domain (although less now than before), the Orphan Drug Act has become an important mechanism to obtain patent like protection on substances that cannot be patented, because of government funded research which has been published in academic journals.

There are many things that the federal government can do administratively to correct the woeful inadequacies of agency policies on the pricing of government funded pharmaceutical inventions. The federal government can develop better approaches to negotiating or setting prices on government funded medical inventions. It can collect better information on the economics of drug development and profits, and it can place more emphasis on competition, by requiring agencies to make findings that exclusive agreements are necessary, or by restructuring the negotiations for exclusive contracts so that companies negotiate on prices *before* partners are chosen for exclusive arrangements (getting more mileage from the *ex ante* competition that exists in these awards).

But there are also many problems that cannot be solved without addressing the reforms in the Bayh-Dole University and Small Business Patent Procedures Act or the Orphan Drug Act -- two deeply flawed laws that have very powerful constituencies. So long as the federal government grants titles to federally funded research conducted by universities and other contract and grant recipients, the Congress will not be able to control prices for many government funded drugs. For example, the 1990 NIH Health Care R&D budget included $4.18 billion in work performed by universities and another $1.8 billion performed by other non-profit institutions.[8] Until the Bayh-Dole Act is changed, the federal government will be severely restricted in its ability to control prices for many important taxpayer-financed drugs inventions.

Consider, for example, the recent agreement between the Scripps Research Institute and Sandoz, a Swiss pharmaceutical firm. Sandoz has agreed to pay Scripps $300 million for the exclusive right to commercialize new technologies developed by Scripps over a ten year period beginning in 1997. Since Scripps receives about $100 million per year in NIH funding, the agreement works like a reverse case of Industrial Policy. The U.S. taxpayers will be funding research that Sandoz will own the rights to, and will be free to sell back to them at unregulated prices. The Sandoz agreement, moreover, is pretty common stuff, distinguished only the amount of dollars involved. Many of the major research institutions now have full time staff whose job is to dream up similar industry partnerships, without regard to the national interest, or the effect of such agreements on consumers or taxpayers.

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[8]This included about $2.5 billion in funding of basic research at universities and colleges, which was nearly half of all federal funds for basic research given to colleges and universities. U.S. Department of Health and Human Services, *NIH Data Book, 1991*, NIH Publication No. 91-1261, (Bethesda, MD: NIH, September 1991).

Appendix C

Notes on the cost of new pharmaceutical inventions

Most recent studies of the costs of developing new drugs have focused on the "green field" cost of drug development. That is, the studies look at the industry's cost of drug development, when the company finances all development, including investments in pre-clinical research. Because there is little data in the public domain on the economics of drug development, the best known research has been carried out by economists who work closely with drug companies, relying upon their consulting relationships to gain access to confidential data. The study which has received the widest exposure on Capital Hill is a 1991 paper by Joseph DiMasi, Ronald Hansen, Henry Grabowski and Louis Lasagna, researchers from Tufts University,the University of Rochester and Duke University.[9] We will refer to this as the DHGL study.

DHGL's analysis has its strengths and weaknesses. The strength of the analysis is the availability of project level information from 99 "new chemical entities" (NCE), provided by 12 U.S. owned pharmaceutical companies. The weakness of the study is the lack of data on pre-clinical investments, which were estimated from aggregate data using assumptions that may or may not be accurate. The bottom line of the DHGL study is that the cost of developing a NCE is estimated to be $231 million. This figure, which is widely quoted, includes both cash outlays, adjusted for inflation, and imputed costs. The imputed costs include an adjustment for the "dry hole" risk of investments, and also the company's opportunity cost of capital, assumed to be a real rate of 9 percent. For example, if a company invests a dollar at a point where the chance of success is only 25 percent, it is counted as four dollars, and then increased again to reflect the opportunity cost of money. In their report, the average inflation adjusted cash outlay of $2.134 million for Phase I trials is adjusted for both risk and opportunity costs, and counts as $17.8 million.

We are currently undertaking an analysis of the DHGL study, as well as other estimates of the costs of development for new drugs, and we are not prepared at this time to provide the Committee with our findings. But there are several factors which the Committee should keep in mind.

1. First of all, the DHGL estimate of $231 million was far higher than previous estimates. For example, a 1987 study authored by Wiggins for the PMA, estimated the cost to be $125 million, and a 1979 study by Hansen estimated the cost to be $54 million (in 1976 dollars). Earlier studies, many of which were flawed on methodological grounds, came up with far lower figures.

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[9]DiMasi, Hansen, Grabowski and Lasagna, "Cost of innovation in the pharmaceutical industry," *Journal of Health Economics*, 10, 1991, pages 107-142.

The fact that the DHGL study was considerably higher than previous estimates isn't itself a criticism of their finding. It is conceivable, for example, the costs of developing new drugs is itself increasing -- as evidenced by the rapid escalation in the prices of new drugs -- as well as the new incentives to invest that those high prices create. If so, Congress should redouble its efforts to control drug prices, particularly when the company does not bear the full costs and risks of development.

2. Next, the Committee may be interested to know that more than half of the $231 million estimated by DHGL was assigned to the opportunity cost of capital. That is, DHGL's estimate that the cash outlays, adjusted for inflation and risk, are $114 million, and the rest represents the profits that the company needs to satisfy investors. Thus, if a company were to receive $231 million in profits from drug sales in its first year, it would have "broken even" on the drug, including the necessary shareholder returns.

3. Third, the Committee will probably be surprised to learn that DHGL assumes that two-thirds of all costs are related to the pre-clinical stages of development. This figure is really the softest part of their analysis, but it does suggest that the cost of developing drugs that have already entered the clinical testing phase is quite low. As a related issue, by the time a drug enters Phase III trials, DHGL conclude that more than 85 percent of the cost of the drug has already been paid for.

Comparing Federal Investments to Private Investments

In comparing the relative contributions of the government and the private sector in the development of new drugs, it is important to recognize ways that industry spokesman manipulate the data. For example, as described above, studies of the industry's costs of developing new drugs typically adjust nominal expenditures for inflation, risk and the opportunity cost of capital. In contrast, the government's costs of drug development are frequently presented in nominal terms, without any adjustments for inflation, risk or the opportunity cost of capital. As a result, many observers have a grossly distorted view of the economic value of the government's drug research investments. For example, some studies report industry Phase I investments at 11 times the initial nominal cash outlays, while government agencies often report drug development costs that only reflect nominal cash outlays to contractors, and ignore the government's costs of intramural research.

To illustrate the types of adjustments that are made, we will assume that inflation is steady at 4 percent, the industry's opportunity real cost of capital is 9 per cent, and the average investment lags behind drug approval are the same as are used by DHGL, as reported in Table 5.

Figures 6 and 7 illustrate the inflation and return adjustments to a dollar of R&D investment, based upon different phases of drug development. Thus, for example, to evaluate the

economic value of government investments in Phase I research, it would be appropriate to multiply the nominal outlays by 2.53 to reflect inflation and the cost of capital.

In Figure 8, further adjustments are made for the risks of development, based upon the DHGL estimates of the probabilities of success at in Phase I, II and III.[10] In Figure 9 is the combined effect of all cost adjustments, including those for inflation, investment return, and investment risk. Thus, for example, in evaluating the economic value of the a government investment in Phase I, it would be appropriate to multiple the nominal cash outlays by 11.

Mathematically, the adjusted cost of drug development investment in Phase j can be expressed in terms of the nominal outlays, the Phase risk given by the probability of success P_j, the rate of inflation i, opportunity cost of capital r, and the years to drug approval, given by N.

$$Adjusted\ Cost_j = \frac{(nominal\ outlay)}{P_j} \quad (1 + r + i)^N$$

[10]DHGL do not provide probability of success for preclinical or NDA phase investments.

The CHAIRMAN. Mr. Love, you mentioned Levamisol. I believe that is a drug that was developed with Federal dollars. It was first given to sheep at 6 cents a tablet. Now it is given to humans, the same tablet, for $6 per tablet. Is this correct?

Mr. LOVE. That is correct. That was $11 million in NIH funding through the Mayo Clinic, and I think, the North Central Cancer Treatment Program.

The CHAIRMAN. We understand that the pharmaceutical company marketing that drug said that they had to pay for the research for the drug. I think the research was paid for by the Federal Government, if I am not mistaken.

Mr. LOVE. Yes, in fact, ironically, in the case of Levamisol, it is the same as Taxol. The company's role in the research that really led to the drug approval was just supplying the drugs.

In Bristol-Myers' case, all they did for the data that was presented to the FDA for the approval of the drug was to supply Taxol for the trials. The Federal Government ran even the Phase 3 trials for Taxol.

In the case of Levamisol, the primary role of the drug company was to provide the drugs.

The CHAIRMAN. Thank you.

Let me ask a question of Caroline Decker. Tell me, Caroline, if you would, what would you say that the normal drug costs for an average AIDS patient that you come in contact with would be?

Ms. DECKER. How about if I give you an example that I put in my written testimony? I'll use the name, Tome, because that is the name he gave me to use.

He has to take 12 doses of different medications per day. We estimated that it would probably cost him $5,000 each month for the medication he is on. He does get some sources of income, but he does go without a lot of times. That is how he survives.

The CHAIRMAN. Are most of these people on Medicaid? I might ask that also of Mr. Hodel. Do you find that those you work with have spent down their assets and now they are Medicaid recipients?

Mr. DECKER. That is sometimes true. You have to be considered to have full-blown AIDS to be on disability. Then you have to be on Medicaid, be approved for Medicaid, in a certain way. I don't want to go into all that, but there are a lot of people that are just on disability that have to find ways, such as a Medicaid spend-down, and so forth. These are still having to find other resources out there. They do have to drop to a limit.

When AIDS comes about, this is a time when they are starting to develop their own careers, their own lives, and they are having to lose their entire lifestyle because of this disease.

The CHAIRMAN. Mr. Hodel, any comments along that line of questioning?

Mr. HODEL. Medicaid eligibility criteria vary substantially State by State. So what we hear from people around the country is that the spend-down process can either be fairly rapid or it can be prolonged, and can involve a substantial fight.

Southern States in particular have fairly stringent Medicaid eligibility. So it can take some time before one is impoverished enough to qualify for Medicaid. It can involve distribution of assets.

It is during that period that people have the most difficulty in purchasing medications, because as one spends down, then you are forced to make a decision between housing costs or medication costs, child care costs or medication costs, food costs or medication costs.

Ultimately, though, we see that 40 percent of PWA's eventually end up on Medicaid one way or another.

The CHAIRMAN. Senator Cohen.

Senator COHEN. Thank you, Mr. Chairman.

We are going to be talking a little bit later about CRADA's. We now have a new acronym to deal with today. As the Chairman said, it deals with the cooperative agreements that are entered into by NIH.

I take it from you, Mr. Hodel, and perhaps Mr. Love, that you don't want to see NIH involved in any kind of price review or enforcement. You would rather see some other agency.

Mr. HODEL. Our view is that the function required is a substantial one, and that NIH's mission is not perfectly positioned to enable it to do it. I am sure that they could develop the expertise, but our view is strongly that the research and regulation of drug approval should be kept separate from the regulation of drug pricing.

Senator COHEN. Would you agree with that, Mr. Love?

Mr. LOVE. I certainly do. I think that the point that Mr. Hodel made is that the mission of the NIH is really different.

The scientists that are working on the development of these drugs lose all perspective on things. They will do anything to see the drug they worked on reach the market. Most of them don't have any interest in looking at the economics of it. They, I think deliberately, sabotaged the fair pricing procedures in order to get out of the job of having to regulate the prices.

Senator COHEN. It seems to me that what we have is a situation in which an agency of the Federal Government is entering into a contractual arrangement with the private sector. They are signing agreements which call for the expenditure of large amounts of taxpayer dollars in these contracts, in which they have no expertise in terms of determining what a fair price for the development of a particular drug is. They have no monitoring, either in experience or staff, and they have absolutely no enforcement.

So we are, in fact, signing agreements on that back sheet, with no understanding of how to really talk about a reasonable price, and no intent of really enforcing it. That is why I think Congressman Wyden used the metaphor about a toll-free highway to the taxpayers' pockets. It seems to me that this is simply that there are no barriers there. There is no enforcement; there is no oversight; there is no way to determine whether or not this is a responsible course of action.

Mr. NADER. Well put, Senator Cohen. I might add, it can be described as a corporate welfare highway, one-way.

What we see here is, in addition to the tragic ordeal of patients either not being able to afford these pharmaceuticals or having to go without, the development of these drugs—the giveaway of these taxpayer assets to the drug companies, with no royalty payments in many cases, and with no price restraints to the consumer.

Because these prices are so high, the burden falls on Medicaid. Who of course pays for Medicaid? The taxpayer. The taxpayer pays going in; the taxpayer pays going out. There are no kinds of restraints that would produce prudence and frugality in, for example, wild promotion budgets, vis a vis doctors by drug companies, etc. So it is really the worst case scenario from an economic point of view and from a patient point of view in terms of the tragedies that the other two witnesses have observed.

Senator COHEN. Assuming that we were to adopt some rule which provided for a royalty payment on the part of the pharmaceutical companies, isn't it reasonable to anticipate they would simply pass that cost on in the form of higher prices without some other mechanism for controlling them?

Mr. Love.

Mr. LOVE. Well, I think you would have to look at the pricing models of the firms. It may be reasonable to assume that some part of the royalty may be passed on. We have never really argued that the royalty should be the first concern of the Federal Government in the technology transfer. We have always focused on the price regulation aspect.

Let me also point out a problem with having the NIH regulate the price. In many cases, the way the drug development process works is that the patent may be held by one company, and the Government may do the research after the patent exists. Because of this, it is important to develop pricing mechanisms which deal with the complex ownership of intellectual property rights for many of these drugs.

Mr. NADER. Another way to look at it is by shortening the patent term and developing compulsory licensing, so that the company will recover whatever costs, but it won't develop a windfall profit in its 10th or 15th year of monopoly patent protection. Unfortunately, Canada, which had the lowest pharmaceutical prices in the Western world, and still does, has just abolished its compulsory drug licensing law on the grounds that it is required under the proposed NAFTA agreement. Congress is only perhaps a few months away from tying its hands under an international trade agreement which would prohibit it from passing any drug patent compulsory licensing law.

The CHAIRMAN. Senator Feingold.

Senator FEINGOLD. Mr. Chairman, with regard to the question Senator Cohen just asked, the obvious problem with the NIH not being the right body to make the regulatory decisions, what type of an alternative do you see for regulation? What type of Government organization should it be? This is directed at Mr. Nader. Then I ask, shouldn't this apply to drugs in general? Is it just NIH-related drugs, or don't we need some sort of pricing board in general?

Mr. NADER. I think when the Government leases land for oil and gas, they get a royalty. I think it is important for a research agency like NIH to be able to get some sort of return for budgetary purposes on its assets that it has used taxpayer funds to develop, and then grant away.

I think your point on why it should just restrict itself to NIH drugs is well taken. I think the Canadian experience in compulsory

licensing after 5 years, which it engaged in until very recently, is a very useful experience to study. The provision of monopolies should be antithetical to conservative doctrine as well as progressive doctrine, in an area of staggeringly upward accelerating drug prices.

Mr. LOVE. I think that you have to look at all drugs. I think that when Government-funded drugs enter the picture, you just simply have to cite it. The agency that regulates the prices has to take into account who paid for the development of the drug.

Mr. HODEL. I'd also like to point out on the NIH's behalf that the research that the Federal Government is involved in is typically high-priority research, like that into AIDS or into cancer. Our view is that it is perfectly appropriate that the taxpayer support such research.

The question of price regulation for those drugs has got to be viewed in context of the whole marketplace. The last thing that we wish to do is to discourage the kind of innovative research that is going on at NIH.

The CHAIRMAN. Could we use the patent as a leverage? Could we reduce the number of years for a patent, or grant a patent 2 years at a time, or use that as some leverage to keep the price in line if the Federal taxpayer absolutely subsidizes the discovery of a drug, and then gives the drug to a pharmaceutical company? Could we use this as leverage?

Mr. LOVE. If the Government holds the patent, they can license it any way they want. You are suggesting amending the patent law like the Canadian system?

The CHAIRMAN. Right.

Mr. LOVE. Yes.

The CHAIRMAN. I'm looking at options. One option, of course, is the royalty. We have discussed a little of that. There is also a price bid. Would it be possible for the companies to come in and bid for a particular product that had been researched and discovered in the NIH or one of the Federal labs? Is that a possibility?

Mr. LOVE. Yes. We've asked David Genesove, a professor at MIT in the economics department, to do a study that will be finished in April, which looks at two things. The first is exactly what you talked about: What opportunities does the agency have when it is in possession of the property rights, either the patent or some other intellectual property? For example, in Taxol, it was just the clinical records that were decisive.

Second, in that stage, to look at whether or not, in the process of doing a license, they can exploit whatever competition exists. What types of contracts would be written which would result in a fair price?

The second part of the study looks at how do you set the price on a drug where the funding is mixed and shared between the Government and the private sector.

The CHAIRMAN. Mr. Nader, let me ask this final question. Is most of the research done by the drug companies, the pharmaceutical companies, on me-too drugs? Is that what you asserted in your statement?

Mr. NADER. Yes. They are basically imitative drugs with a brand name in order to deal with what Chamberlain, an economist at

Harvard, once called monopolistic competition. They are not drugs with significant therapeutic breakthroughs. Me-too drugs, as you called them.

The CHAIRMAN. In your statement, did you say that in 1991, 7 out of 10 of the drugs that came to the market had Federal funding attached to the research? Is this correct?

Mr. NADER. Yes. Of the high priority drugs, classified A, E, and AA, 7 out of 10 were developed with taxpayer, or Federal funds.

The CHAIRMAN. Does NIH have the expertise to decide what we should get back after we license one of these drugs to a pharmaceutical company? Does NIH have business people on the staff to say we ought to get 30 percent in royalties, or we ought to take 50 percent of the patent, or anything of that sort? Do they have the type of expertise?

Mr. NADER. Senator, judging by the contracts that they sign with companies like Bristol-Myers, it is doubtful whether they have any lawyers on staff who would stand in the private sector on charges of malpractice, much less economists.

Mr. LOVE. One thing that we were surprised at was that when we studied all the new cancer drugs that have been invented since 1955, the beginning of the NCI's new cancer program, Bristol-Myers is the marketing company for 33 percent of the 34 drugs the Government financed the development of. They have built a literal oncology empire on Government-funded drugs. Of the 11 drugs, they were not the discovery institution for a single 1 of the 11.

The CHAIRMAN. How does one company move into that position? How does that happen?

Mr. LOVE. I think you should address that to Mr. Chabner, who is going to be a witness today. I think he has been involved in a lot of the negotiations with Bristol-Myers. We have relied, actually, on a lot of his research in identifying the history of the drugs. He is better able to defend that policy than we are.

Mr. NADER. Also, you might want to ask some of Bristol-Myers' so-called competitors to what extent they approve of this intensive relationship between Bristol-Myers and NIH. If you look at the contracts that are drafted, they are so one-sided, and so giveaway prone of the taxpayer assets, that it would be good for the Committee to ask one of the lawyers for NIH to explain how they can in good conscience draft such one-sided, giveaway contracts.

The CHAIRMAN. Thank you. We want to thank this panel. You have made a real contribution to our hearing this morning. You have certainly helped to educate me, and I know our colleagues share in that expression of gratitude to you. We appreciate very much your coming, and we will move to our panel number three. Thank you very much, all of you.

Our next panel is Judith Wagner, Ph.D., U.S. Office of Technology Assessment; and Mr. Peter Arno, Albert Einstein College of Medicine, from Bronx, NY. If you would, come forward, please.

Dr. Arno has concentrated his work on the issues of the development of pricing of AIDS drugs. He has recently written a book entitled, "Against The Odds." I believe he has a copy of it there. It describes how the Government supported the development of many AIDS drugs, including AZT.

Judith Wagner, with the OTA, the Office of Technology Assessment, is just completing a 3-year study on the drug industry. I believe this study has been requested by our friend and colleague, Congressman Waxman, in the House. She is accompanied this morning by Dr. Michael Gluck.

We welcome the three of you. We will call first on Dr. Judith Wagner.

STATEMENT OF JUDITH WAGNER, SENIOR ASSOCIATE, HEALTH PROGRAM, OFFICE OF TECHNOLOGY ASSESSMENT, ACCOMPANIED BY MICHAEL GLUCK, SENIOR ANALYST, HEALTH PROGRAM, OFFICE OF TECHNOLOGY ASSESSMENT

Ms. WAGNER. Thank you, Mr. Chairman.

With your permission, we are going to submit our written comments for the record.

The CHAIRMAN. Without objection, so ordered.

[The prepared statement of Ms. Wagner follows:]

OTA TESTIMONY

Statement of

Judith L. Wagner, Ph.D.
Senior Associate, Health Program
Office of Technology Assessment

and

Michael E. Gluck, Ph.D.
Senior Analyst, Health Program
Office of Technology Assessment

Before the

Senate Special Committee on Aging

On

The Federal Government's Role in New Drug Research and Development: Lessons from Ceredase™

February 24, 1993

Congress of the United States
Office of Technology Assessment
Washington, DC 20510-8025

Mr. Chairman, we are here today at your request to offer testimony on the policy issues raised by our Federal Government's substantial support for and investment in pharmaceutical research. As you know, OTA is completing a study of pharmaceutical research and development (R&D), which will be released in the coming weeks. Though we are unable to comment on the conclusions of that assessment at this time, OTA has separately published a case study of the Federal role in the development of a single very expensive drug: Ceredase™. Our testimony today is based largely on what we learned in the course of that case study about collaborations between the Federal Government and private industry in the discovery and development of new medicines.

Federal Support for Pharmaceutical R&D

The Federal government is the backbone of the country's biomedical research enterprise, with more than $10 billion spent on health-related R&D in 1991. About $7 billion of that spending went to academic and non-profit institutions; the remaining $3 billion was spent on intramural research in Federal research laboratories, primarily NIH.

Most of the Federal government's research affects pharmaceutical R&D indirectly, by advancing the state of knowledge about health and disease. However, OTA estimates that over $700 million was spent in 1989 on direct support for pharmaceutical R&D. These funds include spending on 12 programs whose specific mission is to develop new drugs targeted to important, often life-threatening, diseases. In 1991, NIH had 121 drugs under development, more than any single drug company.

Federal Support for Ceredase™

The power of Federal research to discover and develop important new drugs for people in need is poignantly illustrated by the case of Ceredase™. Ceredase™ is the brand name for alglucerase, a chemical derivative of an enzyme that is missing in people with Gaucher disease. Without the enzyme, glycolipids accumulate in the organs of people with Gaucher disease, causing bone and abdominal pain, anemia, disability, and even death. Between 2,100 and 11,000 people in the United States are believed to have symptoms severe enough to warrant medical intervention. Alglucerase is so far the only effective treatment for Gaucher disease. Periodic infusion with this drug throughout the patient's lifetime is needed to restore function to patients with Gaucher disease.

Federal research personnel and funds were central at each step in the discovery and development of alglucerase.

- NIH researchers identified the enzyme defect that caused Gaucher disease in the early 1970s.

- o NIH researchers developed and patented a method of harvesting the enzyme from human placentae in 1975.
- o NIH contracted with the New England Enzyme Center at Tufts University for the production of research quantities of the enzyme between 1976 and 1981. NIH spent about $1 million for the enzyme over this period.
- o NIH researchers developed a chemical modification of the enzyme that greatly improved its effectiveness. This modified enzyme, identified in the early 1980s, was called alglucerase.
- o Beginning in 1981, NIH contracted with Genzyme Corporation, whose formation in 1981 coincided with the closure of the New England Enzyme Center and whose founders included researchers from the Center, for the production of research quantities of alglucerase. Over the next 11 years, NIH paid Genzyme a total of almost $9 million for the drug.
- o NIH paid for and conducted the clinical studies that were pivotal for FDA's approval of alglucerase in 1991. Almost all of the alglucerase used in these studies was purchased from Genzyme. Genzyme supplied alglucerase free to the NIH for an 8-month period.
- o NIH continues to study the effectiveness of alglucerase in Gaucher disease and to purchase the drug from Genzyme. In 1992, after the drug had been approved for marketing, NIH signed a $2.3 million contract with Genzyme for purchase of alglucerase.

Genzyme Corporation, a young pharmaceutical company headquartered in Cambridge, Massachusetts, also invested in the development of alglucerase. On the basis of information supplied by Genzyme, OTA estimated that Genzyme spent $29 million on R&D and additional funds on manufacturing facilities and equipment[1] between 1981 and 1991, when alglucerase was approved for marketing. A large fraction of the R&D cost incurred by Genzyme was for improving the harvesting, purification and manufacturing process for alglucerase. Genzyme is also actively engaged in the development of a recombinant form of the enzyme, which should be both safer and less expensive to produce.

Genzyme benefited not only from NIH's extensive research efforts but also from laws and policies governing FDA approval of new drugs for life-saving and orphan drugs:

- o Genzyme applied for orphan drug status for Ceredase™ in 1983, soon after the passage of the Orphan Drug Act of 1983, and was granted orphan drug status in 1985. When Ceredase™ was approved in 1991, Genzyme was granted 7 years of exclusive marketing rights for Ceredase™ under the Orphan Drug Act.

1Genzyme shared proprietary data with OTA on the condition that OTA would publish such data only with the company's permission. OTA does not have permission to divulge Genzyme's estimates of its investments in manufacturing plant and facilities.

- Genzyme was permitted to make Ceredase™ available to patients around the country between October 1989 and its approval for marketing in April 1991. Under the FDA's Treatment IND program, Genzyme sold the drug at a price of $3.00 per unit, 86 percent of the price it would charge after approval. Genzyme received over $5 million through this program.
- FDA's review of Ceredase™ was expedited under the Agency's Subpart-E regulations, which call for faster review of drugs for life-threatening illnesses. Ceredase™ was approved for marketing 12 months after Genzyme submitted a new drug application (NDA), compared to an average wait of 30 months for drugs approved through regular channels.

The Federal government's involvement in the development of alglucerase would be a shining example of the benefits of government-industry cooperation were it not for one complication: Ceredase™ is a very expensive drug -- perhaps the most expensive drug ever sold. We estimate that treatment with Ceredase™, including the cost of the drug and its administration, can run from a minimum of $70,000 to more than $500,000 each year. These costs are borne largely by public and private insurers. About 21 percent of patients receiving Ceredase™ were covered by Medicare and Medicaid.[2] About 73 percent of patients receiving Ceredase™ are covered under private health insurance. The high cost of the drug could exhaust or critically reduce some of these people's available health benefits over time.

Although NIH conferred a valuable franchise on Genzyme by sharing its knowledge with the company and paying the company to produce the drug throughout the research period, NIH neither received royalties from Genzyme nor had any say in the price that would be charged for the drug once it was approved. While NIH researchers brought a valuable new therapy to people suffering from a debilitating and life-threatening illness, they did so without any consideration of the financial costs to patients and the public.

Implications of CeredaseTM for Technology Transfer Policy

Ceredase™ was discovered and largely developed before current technology transfer policies were put into effect, but the issues raised by Ceredase™ are just as relevant for drugs discovered with substantial funding from NIH today. In fact, the incentives put in place by the Federal Technology Transfer (FTT) Act of 1986 (Public Law 99-502) for NIH and other Federal research laboratories to patent and license their inventions and to cooperate with private industry on the development of new therapies means that cases like Ceredase™ will become more common, not less common, in the future.

2Although Medicare does not cover outpatient prescription drugs, it does cover any drugs that must be administered under a physician's direction.

The FTT Act gave Federal employees the right to share at least 15 percent of royalties from any licensed invention and it directed agencies to establish cash awards for other personnel involved in productive Federal technology transfer activities. Most importantly, the legislation permits the establishment of formal cooperative research and development agreements (CRADAs) in which a Federal laboratory can collaborate with a partner (e.g., a private company) on R&D. The Federal laboratory can provide personnel, services, equipment or facilities (but not funds), while the collaborating partner can provide funds, personnel, or other resources. Under CRADAs, collaborating firms may have the right to negotiate exclusive licenses to such inventions as part of the agreement itself.

Except for CRADAs, the PHS licensing policy generally restricts exclusive licensing to cases "where substantial additional risks, time and costs must be undertaken by a licensee prior to commercialization." The number of exclusive licenses granted by the Department of Health and Human Services has increased dramatically in the past decade. In 1991, 11 exclusive licenses were granted, compared with only 2 in 1980. Approximately 110 CRADAS are in active status in the Department of Health and Human Services today. As these collaborations mature, and some succeed in producing valuable drugs and technologies, they will add to the growth of exclusive licenses.

Although the FTT Act is silent on the issue of pricing of licensed products, the PHS has adopted a "Fair Pricing" policy for all exclusive licenses, including those granted under CRADAs. Under this policy, the price of commercial products should be commensurate with the "extent of public involvement in the product and the health and safety needs of the public." The policy further states that licensees may be required to provide "reasonable evidence" to support their pricing decisions.

What is a Fair Price?

OTA's experience with Ceredase™ provides some insights into both the need for and the difficulty of determining whether the price that a licensee charges for an drug developed with Federal resources is fair.

The question of "fairness" arises because of the unique characteristics of the medical marketplace. In most sectors of the economy, the market decides whether a price is fair. Competition in the marketplace among different producers of similar products ultimately dictates their prices. Even when a company has a strong monopoly over a product the price may not be very high, because consumers refuse to buy the product if its price is too high.[3]

3Garber, A.M., "No Price Too High?" The New England Journal of Medicine, vol 327, no. 23, Dec. 3, 1992, pp. 1676-1678.

The situation is different for drugs. Because most patients have health insurance that pays for a high fraction of the price of covered drugs, they may be willing to "purchase" a drug even when it is worth less to them than what the seller charges. Most health insurers have little flexibility in choosing what pharmaceuticals they cover and what prices they will pay. Virtually all private insurance contracts with prescription drug benefits agree to cover any medically-indicated FDA-approved pharmaceutical. The result is that when a company has a strong monopoly on a life-saving drug, there is almost no limit to the price it may set.

With Ceredase™, Genzyme Corporation is testing the limits of pricing. Ceredase™ is so expensive that some patients may actually exhaust their lifetime maximum health benefits paying for the drug and its attendant medical care costs. Genzyme has a special program to provide the drug free to patients who have exhausted their benefits or do not have health insurance. Although this program responds in a compassionate way to a real need, it is equivalent in its consequences to offering the patient a lifetime supply of the drug in exchange for the remaining value of his or her insurance coverage. And, patients whose insurance benefits are exhausted are uncovered for all the other medical care they may require throughout their lives.

If we cannot trust the market to automatically set a fair price for drugs developed with substantial Federal support, what are the alternatives? One way to determine whether the price of an NIH-licensed drug is fair is to determine whether the price exceeds the costs to the licensee of developing, manufacturing and distributing it.

Any attempt by NIH or other Federal agency to analyze the costs associated with drugs from licensed NIH technology is likely to face challenges like those we encountered in our study of Ceredase™. Such efforts to examine costs require both relevant expertise and access to appropriate project cost data.

The relevant expertise is particularly important because there are many areas of uncertainty and controversy in estimating R&D and manufacturing costs for specific projects. The Federal government's capacity to conduct such analyses will require professional staff with expertise in corporate management accounting and economics, as well as other areas. The agency responsible for such oversight would need to set forth criteria for maintaining and disclosing project cost accounting at the time a CRADA or license is negotiated.

Having access to relevant cost data is only one challenge facing an agency attempting to determine a reasonable price for an NIH-licensed technology. Here again, the case of Ceredase™ provides a good example.

To determine whether the price of Ceredase™ is too high or too low, one would have to know not only what Genzyme spent to develop and produce the drug and when the company actually incurred such costs, but also the technical risks of failure at each milestone in Genzyme's R&D process and the profit rate required by investors in capital markets for R&D projects similar to Ceredase™. Genzyme's ultimate returns on Ceredase™ also depend on the size of its market and how long the current placental form of Ceredase™ remains on the market before it is supplanted by a recombinant form of the drug. Far more than a textbook knowledge of economics and accounting is needed to address these complexities, but reasonable estimates of each component could be made by technical experts to guide the review of pricing decisions under exclusive licenses.

Detailed cost review is but one of several alternatives for assuring that the prices of NIH-licensed drugs are reasonable. For example, competitive bidding for exclusive licenses, with proposed prices being one of the components of the bid, might work in some therapeutic areas. The development of such strategies requires the ongoing efforts of a professional team whose primary job is to negotiate licenses, keeping in mind the public's dual interest in both medical advance and reasonable prices.

Current NIH Efforts to Implement the Fair Pricing Clause

Although NIH is to be commended for recognizing the potential problem with pricing of NIH-licensed products, so far, NIH has implemented the fair pricing clause in a very few instances, and in none of these instances has PHS attempted to collect or review detailed cost data from companies. For example, in the case of ddI -- an antiviral drug manufactured under exclusive license by Bristol-Myers Squibb -- it appears that the NIH review of its price was limited largely to a public hearing at which the company presented its proposed price. When representatives of patient groups voiced no objections, the price was accepted.

NIH appears to be reluctant to take on the task of reviewing prices of drugs produced under exclusive licenses, and it is not clear whether NIH has the legal authority to demand detailed cost data under the provisions of the FTT Act. At present, the Institutes lack the kind of expertise outlined above to perform such tasks. It is also possible that such a function would conflict with the Institutes' fundamental mission -- to encourage the development of effective new therapies. Consequently, it may be prudent to consider assigning the ongoing responsibility for negotiating exclusive licenses for NIH-developed drugs to another governmental organization.

Ms. WAGNER. As you know, OTA recently completed a study on an effective new orphan drug, known as alglucerase, or by its trade name, Ceredase. This drug is for the treatment of Gaucher's disease, a painful, debilitating, and even deadly disease that afflicts up to 20,000 Americans.

Ceredase was approved for marketing as an orphan drug in 1991, and is manufactured today by the Genzyme Corp. of Cambridge, MA. This drug was discovered and developed largely by researchers at NIH. The list of NIH contributions to the success of alglucerase is impressive, from its first identification to the conduct of pivotal clinical trials establishing its effectiveness. Not only did NIH perform those clinical studies, but it paid Genzyme to produce alglucerase for its research, in effect subsidizing the company's efforts to perfect the complicated production process for this drug.

Because Ceredase is a life-saving orphan drug, FDA policies also helped Genzyme navigate the development process. Ceredase was granted orphan status in 1985, making it potentially eligible for 7 years of market exclusivity once approved. FDA expedited the review of Ceredase under its subpart E regulations. Finally, FDA allowed Genzyme to sell the drug even before it was approved under the Treatment IND Program. Genzyme received over $5 million in revenues before it was ever approved.

All of this Federal involvement with alglucerase would be a shining example of the benefits-industry cooperation were it not for one complication. Ceredase is very expensive, perhaps the most expensive drug ever sold. We estimated that treatment with Ceredase can run from a minimum of $70,000 to more than $500,000 per year for the remainder of a patient's life. Most of these costs are covered by private and public health insurers, including both Medicaid and Medicare.

For all of its developmental help, NIH neither received royalties from Genzyme nor had any say in the price that would be charged for the drug once it was approved. While NIH researchers brought a valuable new therapy to people suffering from a life-threatening illness, they did so without any consideration of the financial costs to patients and the public.

Ceredase offers some good lessons for drugs under development today. The incentives in the Federal Technology Transfer Act mean that cases like Ceredase will become more common, not less common, in the future. NIH now has a fair pricing policy as part of its exclusive licenses and its CRADA's. Licensees may be required to provide reasonable evidence on costs to support their pricing decisions.

Our experience with Ceredase suggests that determining whether the price of a drug is fair is not an easy task. Two necessary ingredients to assessing fairness are: One, having access to good cost data; and two, having the relevant expertise to conduct such analyses. Although NIH is to be commended for recognizing the potential problem with pricing of NIH-licensed products, so far it has implemented the fair pricing clause in very, very few instances. In none of these cases has NIH attempted to collect or review detailed cost data from companies.

NIH appears to be reluctant to take on the task of reviewing prices of drugs produced under exclusive licenses or CRADA's, and

it may lack the legal authority at present to demand such data. It also currently lacks the kind of expertise needed to perform such tasks.

Finally, perhaps most important, it is possible that such a function could conflict with the Institutes' fundamental research missions. So it may be prudent to consider assigning the ongoing responsibility for negotiating exclusive licenses to another Federal organization.

Thank you.

The CHAIRMAN. Dr. Wagner, thank you very much.

By the way, when did you write your book, Dr. Arno?

STATEMENT OF PETER ARNO, ALBERT EINSTEIN COLLEGE OF MEDICINE, MONTEFIORE MEDICAL CENTER, BRONX, NY

Mr. ARNO. The book "Against the Odds" was written over the last 3½ years, and published in 1992 and 1993.

Good morning, Mr. Chairman and members of the Committee. My name is Peter Arno. I am a health economist and associate professor in the Department of Epidemiology and Social Medicine at Montefiore Medical Center and Albert Einstein College of Medicine. It is a privilege to be here today.

As controversy swirls around the pharmaceutical industry, we are repeatedly admonished not to fix what is not broken. Spokespeople are allowed to claim it is one of the most successful and profitable industries in America. In endless advertising and lobbying campaigns they say that substantial investment in research and development justifies the high and rising price of their drugs. We often hear about unsurpassed innovation and global competitiveness that improves the Nation's balance of payments.

The facts beyond the rhetoric are somewhat different. It is not competitive brilliance, but Government-granted monopoly pricing power that accounts for much of the industry's profitability. We have no way of knowing precisely what or how pharmaceutical companies spend their resources on research and development since they refuse to tell us. But we do know that more money goes to marketing, advertising, and promotional activities.

Under current policies, the Federal Government may grant a patent or exclusive license to a pharmaceutical company to distribute and market drugs that have been developed primarily by Government researchers or in a public-private partnership. In so doing the Government is often left with little control over the final price.

This raises two broad questions. The first involves fairness. If a company wants to license a new product from a university or from another firm, it has to pay for the privilege of doing so. Aren't taxpayers entitled to a similar return on their investment?

The second question is economic. When the Government assumes a substantial role in preclinical and clinical drug development, the risks to industry are greatly lessened. Does the rationale remain for the high prices still being charged, especially since much of the Federal investment occurs early in the scientific process when the risks of failure are greatest?

Let me turn very briefly to AZT, the first drug approved for the treatment of AIDS, and still the world's best selling AIDS therapy. The life-prolonging antiviral medication is a good example of how

American citizens subsidize the profits of a private pharmaceutical company. By my count, taxpayers paid for everything from its early preclinical and clinical development to the current subsidy in public treatment dollars.

The Federal Government, largely through the Medicaid Program, is the largest purchaser of AZT in the world. In 1992 approximately 70 percent of the AZT sold in the United States, or $137 million, was paid for by public sources.

Many of you will recall there were no drugs available to treat AIDS when AZT was first approved for marketing in March 1987. Many scientists believed that AIDS was an inherently untreatable illness. When Burroughs Wellcome slapped a per-patient price tag of $10,000 a year on the drug, it was evident to most observers that the cost was not linked to research or development expenses but to the level of patient desperation. Burroughs Wellcome's calculations were simple. Charge what the market will bear.

AZT is an unfortunate paradigm for AIDS drug development for another reason. The Government's work in the early development of this drug was crucial, yet no Government scientist was named on Burroughs Wellcome's patent application. The crucial omission may have cost American taxpayers millions of dollars. Had Burroughs Wellcome acknowledged the Government's role as AZT's true inventor, or at least as a co-inventor, we would have had substantially more control over pricing and access.

The story of Foscavir suggests little has changed in AIDS drugs since AZT. Foscavir was approved in September 1991 to treat cytomeglavirus retinitis, which often causes blindness in AIDS patients. Astra, a Swedish-based pharmaceutical company, set the wholesale price at $21,000 per year. The retail price is much higher. In New York City pharmacies, the average price is $31,235 in 1993.

There is no obvious justification for this extraordinary price. The chemical upon which the drug is based was discovered in 1924, and its antiviral properties have been known for 20 years. According to scientists who helped develop the drug, the molecule is one of the simplest ever approved by the FDA. For this drug, the Federal Government invested nearly $22 million in its clinical development.

Astra claims to have spent $100 million on development of this drug. But as with Burroughs Wellcome, it is impossible to substantiate or discredit that claim because the company refuses to detail its expenditures or to submit to an independent audit. Requests from Congress and the patient community have been met with silence.

Although Foscavir has shown how little industry practices have changed in the course of AIDS drug development, the Federal Government did learn one important lesson from the AZT pricing debacle. Officials at NCI now insert a reasonable pricing clause into some of their cooperative research and development agreements. Unfortunately, the terms in these CRADA contracts are vague and unenforceable. To be effective, reasonable pricing clauses need more teeth. Drug companies must be required to disclose, in confidence, information regarding their actual costs and profit projections.

Reportedly for competitive reasons the drug industry is extremely reluctant to sketch these financial details. However, an agency of the Federal Government with economic and accounting experience could easily be designated to collect and analyze such data. The NIH is certainly capable of assembling the required expertise to perform these functions, but the assignment would go far beyond their scientific mission. I believe the Health Care Financing Administration would be a more suitable agency for the task.

Let me briefly turn to a bolder approach to the control of drug pricing.

The CHAIRMAN. Dr. Arno, I think our time is up. I am going to give you 1 additional minute.

Mr. ARNO. Let me just say that there are two options that have been raised today. One is licensing and royalty payments. About that I would just say that it skirts the issue of fair pricing totally. Given the past record of the drug industry, we can assume that companies will simply inflate their prices to cover the additional expense of royalties.

Second, if companies are unwilling to collaborate with the Federal Government in cooperative research ventures, I think it is fair to say that the Government should produce and market the products itself. This will assure public access to important new therapies at reasonable costs. It may also remind the pharmaceutical companies that the Government has alternatives if they choose to withdraw from these cooperative adventures.

In conclusion, let me reiterate two points. The reasonable pricing clauses inserted in CRADA's have little meaning unless the drug industry is mandated to disclose actual costs and projected profits. Instead of tinkering with exclusive licensing agreements at all, I believe a more effective approach would be to eliminate Government-granted monopolies under most circumstances.

Thank you.

[The prepared statement of Mr. Arno follows:]

Statement of Peter S. Arno, Ph.D.
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Good morning, Mr. Chairman and members of the committee. My name is Peter Arno and I am a health economist and associate professor in the Department of Epidemiology and Social Medicine at Montefiore Medical Center and Albert Einstein College of Medicine in the Bronx. It is a privilege to be here today.

As controversy swirls around the pharmaceutical industry, we are repeatedly admonished not to fix what is not broken. Spokespeople like to claim it is one of the most successful and profitable industries in America. In endless advertising and lobbying campaigns, they say that substantial investments in research and development justify the high and rising price of their drugs. We hear a lot about unsurpassed innovation and global competitiveness that improves the nation's balance of payments.

The facts beyond the rhetoric are very different. It is not competitive brilliance but government-granted monopolies that accounts for much of the industry's profitability. We have no way of knowing exactly what pharmaceutical companies spend on research and development, since they refuse to tell us, but we do know that more money goes to marketing and advertising. Even the much-ballyhooed claims to innovation are subject to question. Between 1985 and 1990, more than 80 percent of all new, FDA-approved molecular entities showed only modest or little therapeutic gains over drugs that were already on the market.

Under current policies, the federal government grants a patent or an exclusive license to a pharmaceutical company to distribute and market drugs that have been developed primarily by government researchers, or in a public-private partnership. Armed with that monopoly, the company can charge consumers whatever it wants; regardless of the taxpayer dollars that have been invested, the government has little control over price.

This raises two broad questions. The first involves fairness: If a company wants to license a new product from a university or from another firm, it has to pay for the privilege of doing so. Aren't taxpayers entitled to a similar return on their investment? The second question is economic. When the government assumes a substantial role in pre-clinical and clinical drug development, the risks to industry are greatly lessened. Does a rationale remain for the high prices still being charged? Especially since much of the federal investment takes place early in the scientific process, when the risks of failure are greatest.

AZT: The First AIDS Drug

As the first drug approved for the treatment of AIDS, and still the world's best-selling AIDS therapy, a look at AZT is instructive. The life-prolonging antiviral medication is a good example of how American taxpayers subsidize the profits of a private pharmaceutical company. By my count, taxpayers have paid for the development and use of this drug at least five times over:

First, when National Cancer Institute grants were funneled to the labs of cancer researcher Jerome Horowitz, who first synthesized AZT in 1964.

Second, in the 1980s, to support the work of NCI scientists, including Sam Broder and Mitch Mitsuya, who proved for the first time that AZT was effective against HIV.

Third, in the government funding of the first phase of AZT trials in human subjects

Fourth, in the liberal tax credits and the exclusive marketing rights provided to Burroughs Wellcome under the Orphan Drug Act, in exchange for producing and distributing the drug. Additional savings came from the business deductions allowed in the federal tax code.

And finally, in the ongoing use of federal dollars to purchase AZT, under the Medicaid program and, to a lesser extent, under the Ryan White Drug Assistance Program. The federal government is the largest purchase of AZT in the world; in 1992, approximately 70 percent[1] of the AZT sold in the United States, or $137 million dollars, was paid for by public sources.

Many of you will recall that there were no drugs available to treat AIDS when AZT was first approved for marketing in March, 1987. Many scientists believed that AIDS was an inherently untreatable illness. When Burroughs Wellcome slapped a per-patient pricetag of $10,000 a year on the drug, it was evident to most observes that the cost was not linked to research or development expenses but to the level of patient desperation. Burroughs Wellcome's calculations were simple: Charge what the market will bear.

AZT is an unfortunate paradigm for AIDS drug development in one other important way. The government's early work in the pre-clinical and clinical development of this drug were crucial, yet no government scientist was named on Burroughs Wellcome's patent application. This crucial omission may have cost American taxpayers millions of dollars (Chart 1). Had Burroughs Wellcome acknowledged the government as AZT's true inventor, or at least a co-inventor, we would have had substantially more control over pricing and access.[2]

Foscarnet: Has Anything Changed?

The story of Foscarnet suggests little has changed in the pricing of AIDS drugs since AZT. Foscarnet was approved in September, 1991 to treat cytomegalovirus retinitis, which often causes blindness in AIDS patients. Astra, a Swiss-based pharmaceutical company, set the wholesale price at $21,000 per year, the retail price is much higher (Chart 2). New York City pharmacies charge an average of $31,235 for a one-year supply.

There is no obvious justification for this extraordinary price. The chemical upon which the drug is based was discovered in 1924 and its antiviral properties have been known for 20 years. According to scientists who helped develop the drug, the molecule is one of the simplest ever approved by the FDA.[3] And the federal government invested nearly $22 million (Chart 3) in foscarnet's clinical development.[4]

Astra claims to have spent $100 million dollars on development. But as with Burroughs Wellcome, it is impossible to substantiate or to discredit that claim because the company refuses to detail its expenditures or to submit to an independent audit. Requests from Congress and the patient community have been met with silence.

In response to criticism, Astra points out that it gives foscarnet away free of charge to people who could not otherwise afford it (Chart 4). The question is why? Along with its public relations value, indigent programs are important to industry because they allow unfair pricing practices to go unchecked. By undercutting criticism on the issue of access, the company is able to extract its price from other payers. The taxpayers who subsidize Medicaid and other government-funded drug purchase plans, and the privately insured, whose premiums rise with every quarter, bear the cost of unconscionably high prices.

Reasonable Pricing Clauses: A Reasonable Way to Go?

Although foscarnet shows how little industry practices have changed in the course of AIDS drug development, the government did learn one important lesson from the AZT pricing debacle. Officials at NCI now insert a "reasonable pricing" clause into the Cooperative Research and Development Agreements (CRADAs) designed to facilitate the commercialization of government research.

Unfortunately, the terms in these CRADA contracts are vague and unenforceable. This was apparent when the first "reasonable pricing" requirement was imposed on the license given to Bristol-Myers in January, 1988 for ddI, another AIDS antiviral drug. Today, little has changed. Bristol-Myers Squibb's January, 1991 licensing agreement for taxol, used to treat advanced ovarian cancer, also includes a "reasonable pricing" clause yet public outrage over the price is mounting.

To be effective, reasonable pricing clauses need more teeth. Drug companies must be required to disclose, in confidence, certain information about pharmaceuticals jointly developed by the government and the private sector. At a minimum, this should include the following data:

- Development costs.
- Marketing and distribution expenses
- The presence and prices of similar competing therapies.
- The likelihood and timing of market entry for additional competing products.
- The projected time it will take to recover development costs.
- The profit margin that has been built into the price

Purportedly for competitive reasons, the drug industry is extremely reluctant to sketch this financial picture. However, an agency of the federal government with economic and accounting expertise could be designated to collect and analyze such data confidentially. The National Institutes of Health is certainly capable of assembling the required expertise to perform these functions but the assignment would go beyond the purview of its scientific mission. The Health Care Financing Administration may be a more suitable agency for the task

Would these disclosure requirements be so onerous that drug companies would choose not to participate in public-private partnerships? Some may opt out. However, it is unlikely that all companies would refuse to participate in CRADAs, despite what a chorus of industry lobbyists might now say. Given the vast level of basic and applied biomedical research conducted by the federal government, and the intensely competitive international pharmaceutical marketplace, there should be no shortage of companies who are willing to collaborate with the government.

A Look at Alternatives

Let me turn now to a somewhat bolder approach to the control of drug pricing. If the government, at taxpayer's expense, has contributed significantly to the development of a new drug, why confer a monopoly on a private company at all? Whether it is done through the mechanism of an exclusive licensing agreement or with a patent, the economic rationale is slender. And there is little evidence that a monopoly is in the public interest

Three strong arguments can be made against a government-granted monopoly:

First, an unregulated monopoly price is higher than the price established through competition. That means that scarce resources are being misallocated and consumers are being held hostage to the marketing and distribution plans of a single corporation

Second, the likelihood that insurance coverage for pharmaceuticals will be broadened in the near future means that monopoly pricing will shift income away from consumers and taxpayers and redistribute it to the pharmaceutical industry.

Finally, the use of public funds gives the government a moral obligation to ensure that products are justly priced and that they are accessible. By suspending the rules of competition, exclusive licenses or patent protection interferes with this mandate.

At present, pharmaceutical companies are not regulated like other government monopolies, such as the public utilities. If the industry wants to operate in a competitive marketplace, then it should live by competitive principles. That means stripping away the artificial protection of government-granted monopolies. If it cannot or will not abide by competitive principles, then the public interest demands that its monopolies be regulated. Industry cannot be permitted to have it both ways.

I would argue that the federal government should grant a monopoly only under two circumstances: 1) if it can be demonstrated that monopoly pricing and profits are needed to offset an extraordinary investment required to bring a new drug to market, or 2) if the potential market for the drug is so small that no company is willing or able to invest the requisite resources in research and development. Neither of these conditions prevailed for AZT, foscarnet, pentamidine, or almost any other approved AIDS drug.

Where these circumstances do not exist, the government should grant non-exclusive licensing agreements when it has been substantively involved in the development of a new drug. The resulting competition makes a lower drug price far more likely.

Two other options deserve mention. If the government develops a new drug therapy or a vaccine, and no private companies are willing to collaborate under the terms proposed here, then perhaps the government should produce and market the product itself. This will assure the public access to important new therapies at reasonable cost. It may also remind pharmaceutical companies that the government has alternatives if they choose to withdraw from cooperative ventures.

Another approach that has been proposed for dealing more equitably with the transfer of federal technology is to require the private sector to pay royalties to the government to compensate for its investment. However, this skirts the issue of fair pricing. Given their past record, we can assume most companies will simply further inflate their prices to cover the additional expense of royalties.

For the past ten years, our society has been trying to come to grips with containing health care costs. Now this has become an imperative. Two independent commissions have been chartered to advise Congress on how to contain expenditures in the two largest segments of the health care market. The Prospective Payment Assessment Commission (PROPAC) has been impaneled to review hospital costs and the Physician Payment Review Commission (PPRC) is studying the price and value of physician services. We can not allow one of the fastest growing components of health care costs — pharmaceuticals — to remain exempt from administrative oversight. In most industrialized countries of the world, some form of control over drug prices is automatic. We ought to do no less for American citizens. It is long past time to make this issue a central part of the dialogue about national health care reform.

In conclusion, let me reiterate two key points. The reasonable pricing clause inserted in CRADAs have little meaning until the drug industry is mandated to disclose actual costs and projected profits. But instead of tinkering with exclusive licensing agreements, I believe a more effective approach would be to eliminate government-granted monopolies under most circumstances. Within the framework of the free enterprise system, competition should rule unless there is good reason to take another approach.

Finally, I would like to commend this Committee for its willingness to take on the tough issue of the pricing practices of the drug industry. Your efforts to transform the process of technology transfer in the public interest are sorely needed and warmly welcomed. Hopefully, these issues will remain on the table as Congress and the new Administration pursue systemic reforms in the health care system during the coming months.

Thank you.

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[1] Personal communication, Fred Hellinger, U.S. Agency for Health Care Policy and Research, February 1993, based on findings from the AIDS Costs and Service Utilization Study (ACSUS).

[2] For more details on the development of AZT and other AIDS drugs see Arno PS and Feiden KL. *Against the Odds: The Story of AIDS Drug Development, Politics and Profits* (New York: HarperCollins) 1993.

[3] Gladwell M. High price of latest drug for AIDS patients decried. *Washington Post* November 12, 1991.

[4] According to a letter from former Secretary Lewis Sullivan to Senator David Pryor dated April 10, 1992.

Burroughs Wellcome AZT Sales
1987-1992 = $1.4 Billion

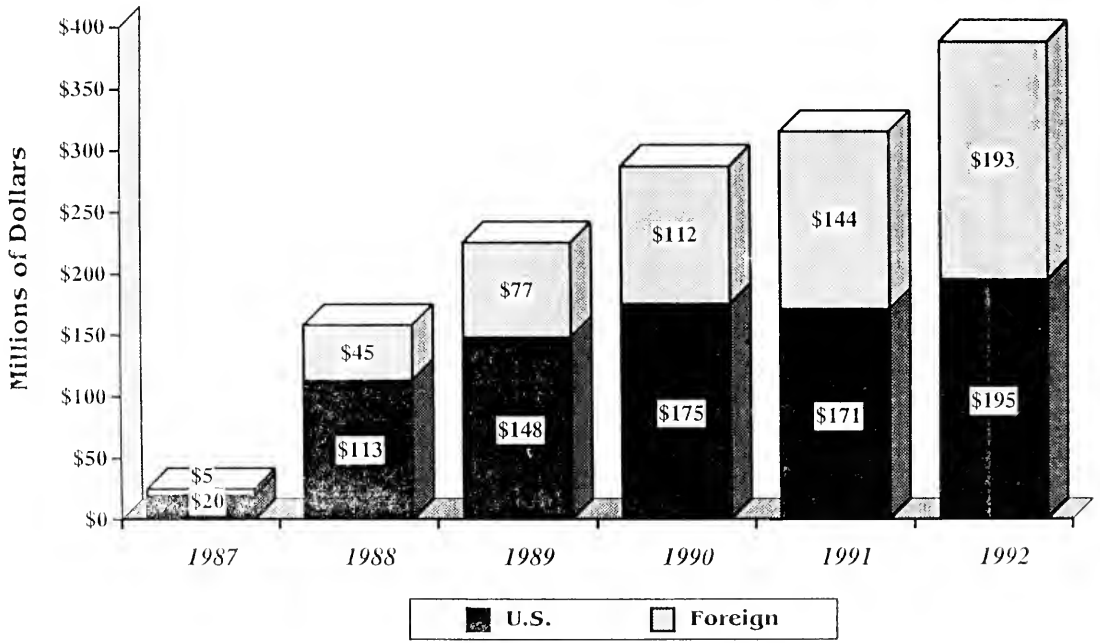
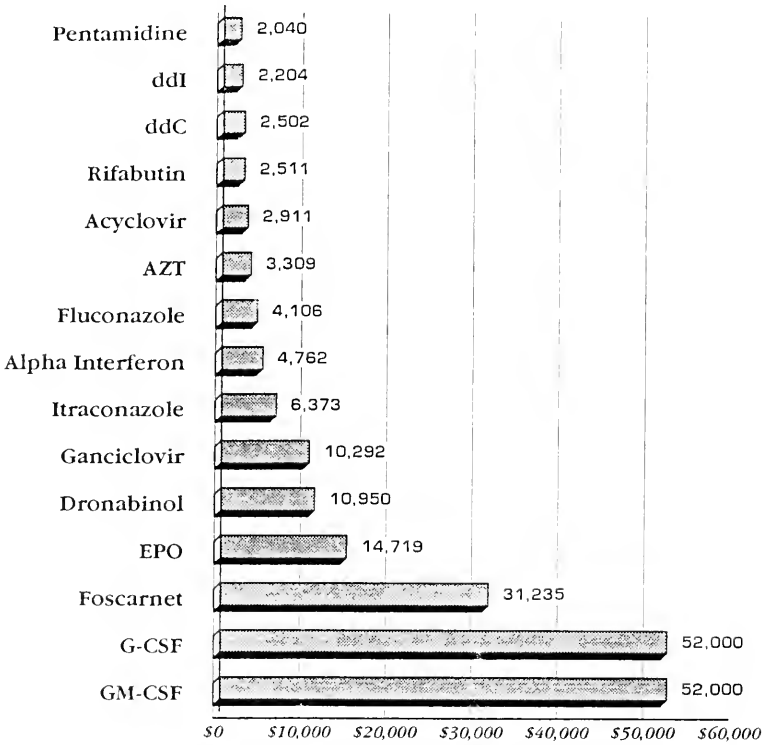


Chart 1

Chart 2

Selected Drugs used to Treat HIV Disease
Retail Cost per Year, dollars



Source: NYC Pharmacies

Chart 3

U.S. Government Expenditures on the Clinical Development of Foscarnet

Total = $22 Million

Government Studies	Government Expenditures (millions)
Intramural (NEI/NIAID/NCI)	$1.700
ACTG 015	$1.350
ACTG 129	$13.40
ACTG 028	$0.206
ACTG 053	$0.138
ACTG 093	$3.900
ACTG 095	$0.596
ACTG 136	$0.160
ACTG 151	$0.413
Total	**$21.863**

Source: Letter from former Secretary of Health and Human Services, Lewis Sullivan to Senator David Pryor, April 10, 1992

Chart 4

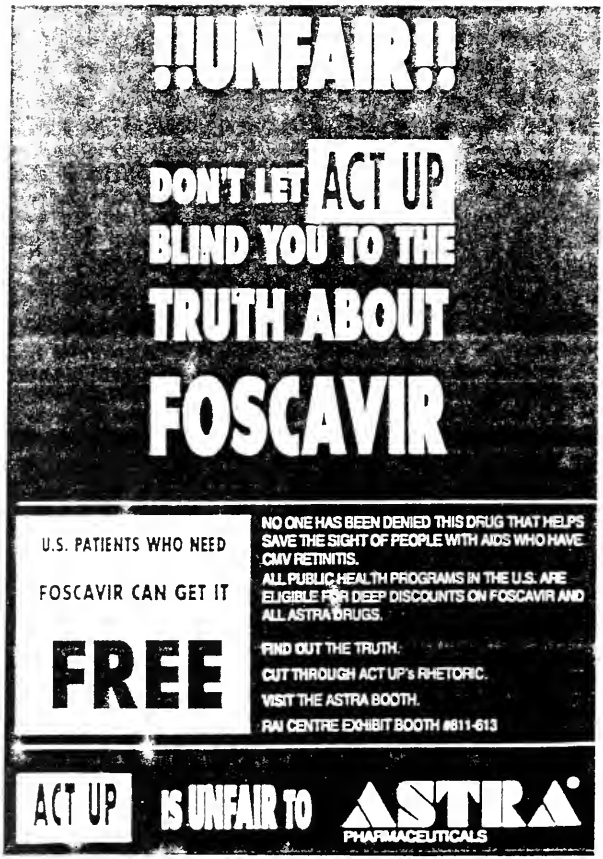

!!UNFAIR!!
DON'T LET ACT UP
BLIND YOU TO THE
TRUTH ABOUT
FOSCAVIR
U.S. PATIENTS WHO NEED
FOSCAVIR CAN GET IT
FREE
NO ONE HAS BEEN DENIED THIS DRUG THAT HELPS SAVE THE SIGHT OF PEOPLE WITH AIDS WHO HAVE CMV RETINITIS.
ALL PUBLIC HEALTH PROGRAMS IN THE U.S. ARE ELIGIBLE FOR DEEP DISCOUNTS ON FOSCAVIR AND ALL ASTRA DRUGS.
FIND OUT THE TRUTH.
CUT THROUGH ACT UP's RHETORIC.
VISIT THE ASTRA BOOTH.
RAI CENTRE EXHIBIT BOOTH #611-613
ACT UP IS UNFAIR TO ASTRA
PHARMACEUTICALS

Chart 5

Ongoing Government-Funded Trials of Selected HIV Drugs

Drug Gov't Trial	Trial Opened
Alpha Interferon	
A1000012	September 1992
ACTG153	November 1991
AIF &Z007	November 1991
ACTG197	October 1992
DDCZ015	June 1992
KAPOS033	April 1992
ACTG206	July 1992
AZT (Retrovir)	
ACTG135	November 1991
AIF&Z007	November 1991
AIF&Z009	October 1992
DDC/Z015	June 1992
ACTG076	January 1991
ACTG082	August 1989
AZ0C0046	June 1991
ACTG161	June 1991
ACTG182	September 1992
AZ000051	December 1992
AZ000041	January 1990
AZ000050	January 1993
ACTG193	December 1992
DIDC003	February 1992
AZ000049	November 1992
ACTG152	September 1991
IVXE5901	September 1992
ACTG168	July 1991
ACTG180	February 1992
BIRG0004	December 1992
BRL&Z001	January 1993
ACTG201	July 1992
ACTG190	December 1992
ACTG176	November 1990
DI&Z006	June 1992
SC&Z0001	September 1992
AZTOX026	November 1990
AZTOX028	February 1992
IL2&Z049	May 1990
L6970006	February 1993
COMPACT1	October 1992
SCF&Z001	September 1992
3TC00003	January 1993
CMVTX044	January 1993
ACTG162	January 1991

Aerosolized penatmidine (Nebupent)

PCPPR035	June 1992
CPCRA013	July 1992
PCPPR032	February 1992

Acyclovir (Zorivax)

COMBO001	July 1991
HERPE012	June 1992
HERPE006	June 1991
HERPE015	December 1992
HERPE013	September 1992
ACTG169	October 1991

Atovaquone (Mepron)
NIAID 1990 CC-164
NIAID 93I-36
FDA 053D
Six additional trials not open to enrollment because they are completed or enrollment is closed

Dronabinol (Marinol)

WASTE022	April 1992

ddC (HIVID)

ACTG197	October 1992
DDCZ015	June 1992
ACTG193	December 1992
DIDC003	February 1992
BIRG004	December 1992
COMPACT1	October 1992
ACTG163	November 1991
LYMPH012	December 1990

ddI (Videx)

ddi00015	August 1992
ACTG176	November 1990
ACTG193	December 1992
DIDC003	February 1992
ACTG194	November 1992
ACTG152	September 1991
IVXE5901	September 1992
BIRG0004	December 1992
DDI00015	August 1992
ACTG176	November 1990
LENT1004	March 1992
COMPACT1	October 1992
CMTVTX044	January 1993
ACTG206	July 1992
ACTG163	November 1991
LYMPH023	June 1992

EPO (Epogen)

AZTOX026	November 1990

Chart 5

Fluconazole (Diflucan)

CAND1009	May 1991
CAND1014	October 1992
CAND1011	May 1992
CAND1016	December 1992
COCC1001	October 1991
COMBO001	July 1991
CRYPC021	October 1991
ACTG174	December 1991
HISTO003	August 1990
MYCOB056	November 1992

Foscarnet (Foscavir)

CMVTX033	March 1991
ACTG228	December 1992
CMTVTX026	Novermber 1990

Ganciclovir (Cytovene)

CMTVTX032	August 1990
CMTVYX044	January 1993
CMTVTX030	November 1990
CMTVTX046	September 1992
CMTVTX042	April 1992
CMTVTX045	August 1992
CMTVTX026	November 1990
CMTVTX047	December 1992
ACTG183	December 1992
CMVPR002	September 1992

Itraconazole (Sporanox)

CAND1013	January 1993
CRYPC021	July 1991
CRYPC020	September 1991
CRYPC015	July 1991

Mycobutin (Rifabutin)
MYCOB056- November 1992

Source: American Foundation for AIDS Research. *AIDS/HIV Treatment Directory*, January 15, 1993. This is not an exhaustive list of trials.

The CHAIRMAN. Dr. Arno, thank you very much. I am sorry I had to cut you off.

Let me ask a couple of questions, then I will yield to my colleagues.

The drug manufacturers are maintaining that they will stop cooperating and will not enter into any agreements with NIH if we try to restrict, or in any way control, the ultimate prices that they can charge. Do you believe that they would actually back away from these agreements and stop this research?

Mr. ARNO. It is clear some would. Some already refrain from cooperating, but I think that is the likely response on the part of the industry. If the Government took seriously producing its own drugs, that is not quite as radical as it sounds. By doing all the preclinical and clinical development work, that is the hard and innovative work. Producing the drug is the easy part. The threat of that alone, I think, would engender further cooperation.

The CHAIRMAN. Let me ask this question jointly to Dr. Wagner and yourself. Recently a spokesperson for the pharmaceutical manufacturers said, and I quote "The U.S. Government has neither the capability nor the expertise to undertake the massive clinical programs and other development activities necessary for drug approval." It appears to me that in the cancer and AIDS arena we are doing most of the clinical work. The Federal Government is doing most of the clinical work. Is that right or wrong? Would you comment, please? Dr. Gluck, if you would like come forward, also, on this.

Mr. GLUCK. Mr. Chairman, if you look at the drug R&D enterprise as a whole, it probably is fair to conclude that industry actually does do the bulk of research and testing. But as you have pointed out and as we have seen here today, in certain areas that we as a society believe are particularly important, AIDS and cancer being two very good examples, the Federal Government actually is the expert for these treatments.

NIH actually does the bulk of organizing, managing, and evaluating of clinical trials. It also has drug development programs whereby they actually test compounds submitted by industry for pharmaceutical activity. It has also been pointed out they do discover many of the compounds themselves.

The CHAIRMAN. Dr. Arno.

Mr. ARNO. In Chart 5 of my written statement, which I have submitted for the record, is an outline of what the Federal Government has done on AIDS research in the clinical trials that are currently underway. With approximately $1 billion a year going to this effort, it is hard to argue that the Government is not substantially involved in AIDS clincial drug development.

The CHAIRMAN. A moment ago Mr. Nader said that 33 of the 34 drugs that have been developed under these arrangements, where the company can sell these drugs produced or clinically researched in the Federal labs, belong to one company. Is that your finding? Is that true? I thought it was spread out more throughout the industry.

Mr. GLUCK. We haven't looked at individual companies in a lot of detail.

The CHAIRMAN. Jamie Love is coming back up to the podium here. He wants to respond. Go ahead, Mr. Love, we are kind of informal around here.

Mr. LOVE. I'm sorry. Actually I was the one who misspoke myself. In my prepared testimony, and the charts and graphs, we had said it was 11 of 34. After I got back and sat someone leaned over to me and said, "33 of 34?" I said, "Did I say that?" I apologize and correct myself.

The CHAIRMAN. No problem. I do that constantly. We are glad that the record is straight. Thank you very much for coming forward on that.

Dr. Arno, it looks to me like there are several hundred ongoing research operations at NIH. Are these cooperative agreements between the industry and NIH? Is this what we are looking at?

Mr. ARNO. No. I think that question would be better addressed to the NIH later in the hearing. To the best of my knowledge, these are Government-run trials, and the drug companies do participate in some of them. But the bulk of the funding for these trials is from the U.S. Government.

The CHAIRMAN. Most of them are NIH supported, is this correct?

Mr. ARNO. They are all NIH supported.

The CHAIRMAN. Does NIH have any business expertise to deal with issues of royalties, patents, and pricing?

Mr. ARNO. As you have heard over and over again, I think that NIH certainly could assemble the expertise if they chose to do so. But it seems that they are reluctant to do that, and I think that we should move that to a different part of the Federal Government. We should not make this sound as if that pricing of drugs is such a black box and so mysterious, and so difficult and complex that it can't be done. The Health Care Financing Administration regulates prices for hospitals, which are not simple institutions in our society. They are now attempting to administer prices for payment of physician services. The next logical step is to do the same for pharmaceuticals.

Ms. WAGNER. Can I make a comment on that?

The CHAIRMAN. Certainly, Dr. Wagner.

Ms. WAGNER. I think it is important to keep in mind Senator Cohen's distinction between the contract negotiations for NIH-developed drugs and the larger issue of whether or not price regulation of drugs as a whole is a reasonable way to go.

I think they are really separate issues. I think the smaller issue, the more confinable issue, is the issue of licensing, where we do have a contract relationship and in which there is the capability to develop a permanent secretariat with the economic, accounting, and biomedical expertise to be able to interact on a reasonably competent basis with the industry to develop fair license contracts.

The CHAIRMAN. Senator Cohen.

Senator COHEN. Thank you, Mr. Chairman.

Dr. Arno, you had me with you until you said let's turn it over to HCFA. This Committee has spent much of its time overseeing the inadequacies of HCFA, as far as its enforcement and oversight responsibilities in guarding the taxpayers' dollars. I'm not sure that is the right solution, but we will examine that in a moment.

Dr. Wagner, my understanding is NIH included this reasonable price clause in Cooperative Research Agreements in only two drugs that have come to market, Taxol and ddI. Is that correct?

Ms. WAGNER. Yes. To our knowledge that is correct.

Senator COHEN. I think in your statement you indicated that for the drug, ddI, they had a public hearing and at no time did NIH consider any of the patient groups objecting to the company's announced price.

Ms. WAGNER. Dr. Gluck, would you answer?

Mr. GLUCK. It is my understanding that actually patient groups were offered an opportunity to speak, but felt that the price was fair. It may be best to direct that question to NIH.

Senator COHEN. Very well.

Let me just ask the general question, why include these reasonable price clauses in agreements, (1) if there is no expertise on the part of NIH to determine what a reasonable price is, if there is no oversight exercise, and if there is no mechanism to enforce the breach of it? Why include it at all?

Ms. WAGNER. I think that this was probably an instance of NIH reacting to public concerns and reacting appropriately and inching its way toward to trying to find a solution. The question is whether NIH itself is in the best position to implement such a solution.

I am not an expert on governmental organization, but I do think that what is needed is permanent organization, not an ad hoc committee on a piecemeal basis for this drug, for this license, and that license. There must be an expertise developed and in place somewhere in the Federal establishment.

Senator COHEN. I agree with you. I just don't know. We will ask NIH this question, but I don't know for example what NIH would obtain from a pharmaceutical company in terms of its pricing data, its capital costs, other factors that would go into determining what a reasonable price would be. I note for example that on page 3 of your statement there is a footnote about how Genzyme shared proprietary data with OTA on the condition that OTA would publish data only with the company's permission. They went on to say OTA does not have permission to divulge Genzyme's estimates of its investments and manufacturing plant and facilities.

Ms. WAGNER. OTA was doing a study. OTA was not negotiating a license. OTA had absolutely no power to ask or demand information in response for some benefit to give out. Genzyme was very cooperative, given those constraints.

If NIH or some other organization were negotiating a license for a very valuable product and was trying to essentially trade off fairness to the company with fairness to the public, certainly I believe that some agency—we have a Defense Department that negotiates contracts all the time—in the HHS or elsewhere could assemble the cost accounting, economic, and even biomedical research competence to be able to set up criteria for what kinds of costs should be collected and what format, throughout the development of the CRADA or the product under the license. Then they could deal with some of the very sticky issues of risk, timing, and ultimate market size that all go into the question of whether or not a price is reasonable.

Senator COHEN. Dr. Arno, I gather from your statement you don't think we should have these arrangements at all because they provide for a monopolistic arrangement that cuts out other potential competitors.

Mr. ARNO. In my written statement I argue that in most cases that is true. But if a company could demonstrate that an extraordinary amount of resources were necessary to bring a drug to market, and can show what those figures are, an exclusive license would be legitimate and in the public interest.

I just think that if the Government does the major part of the innovation, why not let the Government license the drug out and let the competitive forces work and help to lower the price?

Senator COHEN. If we were to establish another entity to take on the responsibility of reviewing the price of drugs that are developed under these exclusive licenses, should NIH continue to include the reasonable price clause in the contract, the CRADAs? I mean, why give the responsibility to NIH to include them?

Mr. ARNO. I think that it is pretty clear that they should not have that responsibility.

Could I just respond to one last thing you mentioned? Dr. Wagner spoke to this. The reasonable price clause was instituted the very first time with DDI. It was very much a reaction to what happened with AZT.

The CHAIRMAN. Senator Feingold.

Senator FEINGOLD. No questions.

The CHAIRMAN. One final question: In many drug pricing systems we find that—the United States, the American consumer, pays more for our drugs than any other industrialized nation. Is this true in AIDS and cancer drugs? For example, can we go to Mexico and buy these drugs less expensively, or are they about the same price? What is the price variations between foreign countries versus ours? Do you have any comments on that?

Ms. WAGNER. We haven't studied international price differences in drugs, so we can't comment on that.

The CHAIRMAN. Dr. Arno, do you have any comments?

Mr. ARNO. To the best of my knowledge, many AIDS drugs are available at much lower prices in foreign countries. In fact, there are buyers' clubs organized by patients and other people that import those because of the lower price.

The CHAIRMAN. We had a witness a year or two ago, I believe, Senator Cohen, who testified before the Committee that she had gone to Europe and bought some of the drugs and brought them back to dispense to AIDS patients. Is this still a practice? Is this happening? Mr. Hodel probably could have answered that question. I see him nodding affirmatively. I wish you would come forward. I think this is a critical part of this finding today.

Mr. HODEL. I may not give you the answer you want to hear. The fact is that most AIDS drugs really split into two different kinds of drugs: Drugs that are used to treat HIV infection, of which there are very few; then all of the drugs that are used to treat various opportunistic infections, and that sort of supplemental therapies.

AIDS drugs themselves, AZT, ddI, and ddC, are actually not available in many countries around the world. In those countries

where they are available, we have seen that the prices are consistent with those charged in the United States, or higher.

With respect to other drugs that are used in the treatment of HIV, but not necessarily to treat HIV, the price fluctuates wildly depending on the drug. Some drugs, for example Levamisol, are available in Mexico for a tiny fraction of the cost in this country—in the neighborhood of 15 or 20 cents a pill.

The CHAIRMAN. What about Foscavir?

Mr. HODEL. Foscavir is priced consistently in its worldwide market.

What we have seen, generalizing, the new, sort of highend drugs, like Foscarnet, tend to be expensive wherever they are produced. Pentamidine is perhaps the best example, and was the drug about which I testified before this Committee a few years ago.

Pentamidine is available in this country for in the neighborhood of $75 per dose, and is available in Europe for about a third of that price. The price has fluctuated as high as five to one, but it is an isolated incident.

The CHAIRMAN. I want to thank you for coming back to the witness table. We thank all of our witnesses this morning. You have made a real contribution to our hearing. We appreciate your attendance very much.

Now, we are going to call our fourth panel. We are going to hear now from NIH: Dr. Bernardine Healy, the Director of NIH, the National Institutes of Health; and Dr. Bruce Chabner, who is Director of the Division of Cancer Research of the NIH. We are very, very proud to have both of you here.

You have heard a great deal about NIH thus far in the hearing. We look forward to your statements, and we hope you will help with the 4-minute rule. I am sure that questions will follow.

STATEMENT OF BERNARDINE HEALY, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD

Dr. HEALY. Senator Pryor and members of the Committee, it is a national dilemma that Americans of all ages and many walks of life are intimidated by the escalating cost of health care. Our valiant efforts at NIH to advance the science of medicine will be futile if our discoveries are out of reach for our patients who need them.

In my capacity as Director of the National Institutes of Health, as a physician, and as a mother, I applaud your efforts to focus the Nation's attention on these issues.

In specific response to the questions raised by the Committee about the Federal Government's role in new drug research, I will very briefly touch on three issues: First, the nature, scope, and purpose of cooperative agreements between NIH and pharmaceutical manufacturers and how they relate to the mission of the NIH; second, the specific steps taken by NIH to insure that there is a return on public investment; and finally, the extent to which as a research agency has a role in the drug-pricing debate.

The mission of the NIH is the pursuit of science to improve the health of the American people. The NIH is the hub of our Nation's vast network of biomedical research. Eleven percent of NIH's total budget of $10 billion supports our intramural research program, but more than 80 percent of our budget supports research con-

ducted in virtually all major public and private research institutions throughout the United States. The science base developed by NIH in pursuit of her mission has become the engine driving our U.S. biotechnology industry, creating lifesaving products and thousands of jobs.

The legislative infrastructure that has fostered the strong partnerships between federally funded science and U.S. industry includes the Bayh-Dole Act of 1980, the Stevenson-Wydler Act of 1980, and the Federal Technology Transfer Act of 1986. The Bayh-Dole Act authorizes Federal grantees to own inventions developed with taxpayers' money, and allows grantee institutions to assume responsibility and reap the benefits of commercialization. The Act identifies several important principles for the transfer of technology to encourage the participation of U.S. industry and, specifically, small businesses. The Act also promotes free competition and enterprise, public availability of inventions, and perhaps most importantly, specifies public protection against non-use or unreasonable use of inventions.

In 1986, through the FedTech Act, some of the authorities provided to Federal grantees were extended to Government laboratories. This Act encourages Federal scientists to license and patent their discoveries and enter into cooperative research and development agreements, the CRADAs, with the private sector.

I want to note, especially in the context of this hearing, that these laws and regulations never addressed the issue of reasonable pricing of products developed through such partnerships. The notion of reasonable pricing as part of technology transfer with industry did not arise until 1989. At that time the reasonable pricing concept was included in NIH model CRADAs and patent licensing agreements, and not throughout the Government. NIH took this action back then, even though there was no requirement to do so, because NIH was outraged by the $8,000 annual price for AZT, a drug co-developed by NIH with taxpayers' dollars. To my knowledge, NIH is the first and only Federal laboratory that has addressed the issue of pricing in a CRADA or license agreement.

Several benefits have accrued to the public by including a reasonable pricing clause in the model CRADA. It has put the industry on notice that future collaborations with NIH research must acknowledge the public investment. This acknowledgement, in our brief experience, can mean reasonable price, access for the indigent, compassionate use availability, and access for those otherwise unable to afford the medication. But remember, these mechanisms are only applicable to discoveries within our Federal NIH laboratories which comprise 11 percent of our portfolio. They do not apply to research conducted by our grantees.

But let me also emphasize that the major way in which NIH contributes to restraining the price of pharmaceuticals is through our diversified research portfolio, intramural and extramural. Discovery and development of competitive products are a major factor in determining price. All three drugs approved for use in the treatment of AIDS, have been developed by the NIH and by different pharmaceutical companies. These prices progressively have come to market at a lower price, and we believe competition has been part of it.

We also have similar hopes for a family of drugs for use in treating refractory ovarian cancer, namely Taxol, the drug Taxatir, and other low cost alternatives to the natural substance that are in development.

Thus the maintenance of a diverse research portfolio and the licensing of competing products resulting from our efforts may in fact be our most important contribution toward restraining the price of pharmaceuticals. NIH is actively engaged in defining its role in developing pricing strategies for products developed from NIH research that reflects fairly on the public contribution.

At our December meeting of the Advisory Committee to the Director, a distinguished panel of outside experts discussed this matter extensively. The discussion brought out a number of policy issues materially affecting our fundamental research mission and our technology transfer mandate. While there appeared to be broad agreement that the public investment in marketed products and therapies should be reflected in some manner, most of the Advisory Committee members strongly believed that NIH should not assume the role of a regulatory price-setting agency.

The CHAIRMAN. We are going to have to conclude your statement. We will put it in the record. If you would like to conclude it, I'll give an extra minute.

Dr. HEALY. One thing I can assure you of now, however, is that NIH can contribute to assessments of pricing by providing expert technical advice of the relative merits of various products, the difficulty of their discovery, and by informing policymakers and potential regulators on the costs of NIH's role in the co-development of such products. In the past NIH has provided such technical information to agencies with regulatory mandates.

In conclusion, Mr. Chairman, technology transfer is of strategic importance to the NIH. Partnerships with industry are of strategic importance. But most importantly, if the fruits of our research do not reach the public we serve, for whatever reason, including cost, we have failed in our mission. Our core goal is to conduct medical research to improve life for the American people.

I look forward to working together to find ways of assuring that fundamental discoveries which improve and save the lives of all Americans, young and old, will be achieved.

Thank you.

[The prepared statement of Dr. Healy follows:]

ORAL STATEMENT
BY
DR. BERNADINE HEALY
DIRECTOR
NATIONAL INSTITUTES OF HEALTH
BEFORE THE
SENATE SELECT COMMITTEE ON AGING
FEBRUARY 24, 1994

Senator Pryor, before I begin, I would like to recognize your leadership -- both on this Committee, and earlier as a member of the Pepper Commission -- in search of meaningful solutions to the burden of health care costs on working American families. It is a national dilemma that Americans of all ages, and many walks of life, are intimidated by the escalating cost of health care. Our valiant efforts at NIH to advance the science of medicine will be futile if our discoveries are out of reach for our patients who need them. In my capacity as Director of the National Institutes of Health, and as a physician and mother, I applaud your efforts to focus the nation's attention on these issues.

The Pepper Commission acknowledged the need for a renewed commitment to biomedical research as a fundamental component of containing health care costs. Particularly in view of the anticipated growth in our elderly population, NIH efforts to enhance the independence of older Americans, and to find new cures and treatments for chronic and dehumanizing illnesses will eventually help ease the financial burdens of long-term care. I would like to supply for the record our publication, **Cost Savings Resulting From NIH Research Support**, that provides specific examples of NIH research which has resulted in new treatments that cut health care costs by hundreds of millions of dollars.

In specific response to the questions raised by this Committee about the federal government's role in new drug research, I will discuss three issues: First, the nature, scope, and purpose of cooperative agreements between NIH and pharmaceutical manufacturers, and how such agreements relate to the fundamental NIH mission; Second, the specific steps taken by NIH to ensure that the public investment in research provides a meaningful return to the taxpayer; And finally, the extent to which NIH as a research agency has a role in the drug pricing debate.

The mission of NIH is the pursuit of science to improve the health of the American people. The NIH is the hub of our Nation's vast network of biomedical research. Eleven percent of NIH's total budget of $10 billion supports our intramural research program which includes over 5,000 doctoral level scientists and physicians. More than 80 percent of the NIH budget supports research conducted in virtually all major public and private research institutions throughout the country. The science base developed by NIH in pursuit of her mission has become the engine driving our U.S. biotechnology industry, creating life saving products and thousands of jobs.

The legislative infrastructure that has fostered the strong partnerships between federally funded science and U.S. industry includes the Bayh-Dole Act of 1980, the Stevenson-Wydler Act of 1980, and the Federal Technology Transfer Act (FTTA) of 1986. The Bayh-Dole Act authorizes federal grantees to own inventions developed with taxpayers' money, and allows grantee institutions to assume responsibility and reap the benefits of commercialization. The Act identifies several important principles for the transfer of technology to encourage the participation of U.S. industry and, specifically, small businesses. The Act also promotes free competition and enterprise, public availability of inventions, and perhaps most importantly, specifies public protection against non-use or unreasonable use of inventions.

In 1986, through the FTTA, some of the authorities provided to federal grantees were extended to government laboratories. This Act encouragea federal scientists to license and patent their discoveries and enter into cooperative research and development agreements (CRADAs) with the private sector.

I want to note, especially in the context of this hearing, that these laws and regulations never addressed the issue of "reasonable pricing" of products developed through such partnerships. The notion of "reasonable pricing" as a part of technology transfer with industry did not arise until 1989. At that time the "reasonable pricing" concept was included in NIH model CRADAs and patent license agreements. NIH took this action back then, even though there was no requirement to do so, because NIH was outraged by the $8,000 annual price for AZT, a drug co-developed by NIH with taxpayera' dollars. To my knowledge, NIH is the first and only federal laboratory that has addressed the issue of pricing in a CRADA or license agreement.

Several benefits have accrued to the public by including a reasonable pricing clause in the Model CRADA. It has put the industry on notice that future collaborations with NIH research must acknowledge the public investment. This acknowledgement, in our brief experience, can mean reasonable price, access for the indigent, compassionate use availability, and access for those otherwise unable to afford the medication. But remember, these mechanisms are only applicable to discoveries within our federal NIH laboratories which comprise about 11 percent of our portfolio -- and not to research conducted by our grantee institutions.

But let me also emphasize that the major way in which NIH contributes to restraining the price of pharmaceuticals is through our diversified research portfolio -- both intramural and extramural. Discovery and development of competitive products are a major factor in determining price. All three drugs approved for use in the treatment of AIDS, have been developed by NIH and subsequently licensed by competing pharmaceutical firms: AZT by Burroughs-Wellcome; ddC by Hoffman-LaRoche; and, ddI by Bristol Myers-Squibb. ddI was the first NIH licensed drug to come to market with a "reasonable pricing" clause. It debuted at an average price of approximately 20 percent of its predecessor AZT.

Likewise, we have similar hopes for a family of drugs for use in treating refractory ovarian cancer. Namely, Taxol and the drug Taxotere, which is still in development, as well as other low cost alternatives to the natural substance. Thus, the maintenance of a diverse research portfolio and the licensing of competing products resulting from our research efforts may, in fact, be our most important contribution toward restraining the price of pharmaceuticals.

NIH actively engaged in defining its role in developing pricing strategies for products developed from NIH research that reflect fairly on the public contribution. At our December 2nd meeting of the Advisory Committee to

the Director (ACD), a distinguished panel of outside experts discussed and evaluated the complexities of NIH participation in the pricing of cooperatively developed products. The discussion brought out a number of policy issues materially affecting both our fundamental research misaion and our technology transfer mandate. While there appeared to be broad agreement that the public investment in marketed products and therapies should be reflected in some manner, most of the Advisory Committee members strongly believed that NIH should not assume the role of a regulatory price-setting agency. These issues are being further pursued by NIH's Office of Technology Transfer and a task force under the auspices of NIH's Science Policy Studies Center. We plan to develop some policy options to consider at our spring meeting of the ACD.

One thing I can assure you of now, however, is that NIH can contribute to assessments of pricing by providing expert technical advice on the relative merits of various products, the difficulty of their discovery, and by informing policy makers and potential regulators on the costs of NIH's role in the co-development of such products. In the past, NIH has provided auch technical information to agencies with regulatory mandates such as tha FDA and HCFA.

In conclusion, Mr. Chairman, technology transfer is of strategic importance to the NIH. But most importantly, if the fruits of our research do not reach the public we serve for whatever reason, including coat, we have failed in our mission. Our core goal is to conduct medical research to improve llfe for the American people. I look forward to our continued work together to find ways of assuring fundamental diacoveries and providing accesa to the use of those discoveries which improve and save the lives of all Americans -- young and old. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Doctor.

Dr. Chabner, we welcome you this morning.

Sorry I had to cut you off, Dr. Healy. We will put your entire statement in the record, and we will have questions in a moment.

STATEMENT OF DR. BRUCE CHABNER, DIRECTOR, DIVISION OF CANCER TREATMENT, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD

Dr. CHABNER. Senator Pryor, I am Bruce Chabner. I am a physician and director of the Cancer Treatment Program at the National Cancer Institute. I am pleased to appear today to describe to you our role in the development of new drugs for cancer and AIDS.

Since its creation in 1937, our mission has been to conduct and support research to alleviate suffering and death from cancer. More recently, we have joined the fight against AIDS.

During the mid-1950's it became clear that the private sector was not likely to commit resources required for a comprehensive drug screening and development program in cancer. Therefore, in 1955 the Federal Government established within the NCI the Cancer Chemotherapy National Service Center. Today our drug development effort resembles the essential program conceived in 1955, but with modifications that reflect the dramatic expansion of knowledge of cancer biology and biotechnology in recent years.

A key feature of that program is that we acquire candidate compounds from many sources: from our contractors, who search for novel agents in plants and marine organisms; from academia, and from industry. We conduct initial screening for activity at a cellular level. Positive compounds undergo a rigorous and complex series of tests in the laboratory. If sufficiently active in the clinic to carry out this extensive testing program, we've developed a network of drug evaluation groups in academic institutions throughout the United States.

These investigators provide a unique resource for testing new cancer drugs. Companies or nonprofit institutions may have access to this resource at any point in the development process, from the earliest preclinical work to clinical trials in large patient populations. Compounds discovered by our investigators on the Bethesda or Frederick campuses of NIH can also readily enter this system.

I would like to emphasize that we have dual purpose in this drug development process. We want to develop new therapies and make them available to the public as quickly as possible, and secondly, we have a fundamental research mission to generate new knowledge as to why drugs work and why they fail.

Thus Government scientists conduct an extensive program of research associated with these clinical trials and with the development and discovery efforts for new drugs. This is different but complements traditional drug development programs in industry. However, our system will only bring us to a certain point in the drug's development. We do not have the resources, the infrastructure, or the expertise to mass produce and market new pharmaceuticals. For this we need an industrial partner.

Under the authority of the Stevenson-Wydler Act and the Federal Technology Transfer Act we have the responsibility to transfer

our technology to the private sector. In the area of drug development this is effected by licensing those compounds which have patents, or for compounds lacking patent protection, through the CRADA mechanism.

The actual terms of each license or CRADA depend on a number of factors, including, for example, who owns the agent, what potential hurdles there lie in its development, and its potential in treating cancer or other diseases. The CRADA most recently was used to develop the drug Taxol, which did not have patent protection, and which has proven to be effective in women with ovarian and breast cancer. Without the CRADA mechanism, Taxol would not be available to American women today.

NCI scientists have discovered several new anti-AIDS drugs as well, including ddI and ddC. We have considered a strategy for licensing these agents that would insure access of all AIDS patients to these drugs. Both were potential competitors to AZT. The price of AZT, as has been stated here, was widely viewed as excessive. In recognition of the public investment in the development of these anti-AIDS drugs, NCI modified its standard CRADA and licensing agreement several years ago to include a requirement that our collaborators acknowledge this investment in determining a fair market price.

Further we have adopted an active strategy of fostering competition and diversity so that we encourage the placement of multiple agents in the marketplace for the same medication. The end result is that the three AIDS drugs now being marketed and developed by NCI and NIAID are now being marketed by three competitive companies. Similar competition has been encouraged in the development of Taxol. We are actively collaborating with a French company, which has an analog of Taxol, and we expect it will soon enter the marketplace.

My remarks have concluded.

[The prepared statement of Dr. Chabner follows:]

Testimony of

Dr. Bruce Chabner
Director, Division of Cancer Treatment

Good morning, Senator Pryor and members of the Committee. I am Dr. Bruce Chabner, Director, Division of Cancer Treatment, National Cancer Institute (NCI). I am pleased to appear today to describe for you NCI's role in the development of new drugs for cancer and AIDS.

The National Cancer Institute was created in 1937 as the first categorical institute of the National Institutes of Health (P.L. 244). Its purpose was "to provide for, foster, and aid in coordinating research relating to cancer." Today, our purpose has expanded to include: "the conduct and support of research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients." However, our fundamental mission remains the same: to alleviate suffering and death from cancer through the generation of knowledge, and to transfer effectively that knowledge to the American people.

Drug Development

As Director of the Division of Cancer Treatment, I have primary responsibility for NCI's drug development program. Drug development is a broad term, encompassing the full spectrum of events from acquisition of materials for screening to carefully controlled clinical trials in patients. To appreciate fully the current approach to cancer drug development, it is important to understand how our mission has evolved. Cancer drug development presents many formidable challenges. Traditional drug development models that were used for antibiotics, psychoactive agents, and cardiovascular drugs are difficult to apply to this disease. Our objective is to find drugs that will selectively kill malignant cells without intolerable harm to the normal cells necessary for life. The similarities of normal and malignant tissues complicate this effort. In addition, cancer cells have the ability to mutate rapidly and to develop resistance to treatment. These are the same challenges that we encounter today with AIDS. During the 1950's, it became clear that the private sector would not commit the resources required for a comprehensive cancer drug screening and development program. Therefore, in 1955 the Federal Government established within the NCI the Cancer Chemotherapy National Service Center. This center included all components required for a preclinical drug development program: it was able to obtain and screen new

compounds; develop analogues of active compounds; and conduct toxicology, formulation, and animal pharmacokinetics (studies prior to any testing in humans). Today, NCI's system continues to play a central role in cancer drug development, with refinements and improvements that reflect the dramatic changes in biotechnology in recent years.

The first step in preclinical drug development is acquisition of compounds to test their potential anti-cancer properties. NCI has several mechanisms for acquiring agents. We have an active collection program that searches for natural products throughout the world, including marine life. For example, Taxol®, active against ovarian cancer and possibly breast cancer, was originally isolated from specimens collected by an NCI contractor under one of our acquisition contracts. All samples collected are now tested against a panel of human tumor cell lines to determine their potential as anti-cancer agents. We also test compounds sent to us from academic scientists and industrial sources.

Once candidate compounds have been identified through the screening process, a series of other tests are conducted to scale up synthesis, and to determine toxicity, mechanism of action, pharmacology, and formulation for clinical administration. In some cases, development of a new anti-cancer agent requires highly complex and sophisticated research in which no routine test is available. Such work may be encompassed within the investigator initiated research programs of scientists either working directly for the government or receiving government grants. Other times, development may be straightforward or routine and can be conducted as part of a contractual screening program available to government, academia, and the private sector alike. These tests are completed prior to any use in patients to ensure the drug's safety for use in humans. When all preclinical testing has been completed, the drug sponsor files an Investigational New Drug (IND) application with the Food and Drug Administration (FDA) for approval to administer the drug to patients in a carefully controlled setting and under pre-established guidelines as set forth in a research protocol. Since 1955, NCI has clinically tested over 450 new agents, and has played a role in the discovery or development of most of the approved cancer drugs currently on the market today. Compounds may enter the system at any point in the development scheme, from early preclinical evaluation to clinical trials.

In addition to its preclinical drug development capability, NCI has a large clinical trials network to move promising new agents into patient testing. Small pilot studies can be undertaken at NCI's Clinical Center, at the nation's regional cancer centers, or within our national cooperative clinical trials groups. Once a safe dose is established, broader studies requiring large numbers of patients are conducted by the NCI Clinical Cooperative Groups, the Community Clinical Oncology Program, and the Comprehensive and Clinical Cancer Centers which are capable of rapid accrual of large numbers of cancer patients. These

clinical resources represent a unique and valuable resource for the testing of agents discovered by NCI, by its grantees, or by industry. Our commercial partners can enter this clinical trials systems at any of several points, depending on their own resources, NCI's level of interest in their compounds, and the interest of NCI-supported researchers.

Since our fundamental purpose is to generate knowledge that can improve the treatment of cancer, we have a strong interest in exploring the possible anti-cancer activity of a new drug against a variety of tumors, in different dosages, and in combination with other agents. We seek to understand in scientific terms the reasons for a drug's success or failure. This objective differs from the aim of industry, which seeks rapid regulatory approval of its new agents as its primary goal. Thus, NCI researchers have the flexibility to conduct the studies that may bring about fundamental advances in our ability to treat cancer, whereas often industry would not make such an investment, as it involves risk and diverts resources from the goal of regulatory approval.

All of the steps outlined above, if successful in identifying an active agent, lead to a successful New Drug Application to the FDA. While NCI has considerable experience conducting research on investigational new drugs, as a research institute, we are not able to mass-produce and market products. This is especially true when large scale acquisition and bulk production of natural products is involved. Technology transfer to the private sector is required to ensure that new drugs are quickly made available to the patients who need them. For agents discovered and developed by NCI, the timing and extent of NCI collaboration with an industrial partner may depend on the therapeutic promise of the agent, the existence of prior intellectual property rights, the relative difficulty of production, the potential market, and likely competitors already on the market or under development. Therefore, for a new product discovered by NCI scientists to be approved for commercial use and made widely available to patients, an industrial partner is required.

Technology Transfer

Collaboration between NCI and the private sector is based on several legislative authorities. These include the Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480), the Bayh-Dole Act of 1980 (P.L. 96-517), the Federal Technology Transfer Act of 1986 (P.L. 99-502) that amended the Stevenson-Wydler Act, and Executive Order 12591.

Since the passage of these Acts, it is a national policy to transfer federally-owned or originated technology to the private sector whenever possible and appropriate. The Bayh-Dole Act extended this policy to technology developed with federal funding, such as grants or cooperative agreements. The Acts also encourage, as a national policy, joint research and

development projects between government laboratories and industry. Indeed, technology transfer is a duty of each laboratory. NCI has followed the policy of seeking partners in private industry to commercialize its discoveries and inventions. Our objectives in doing so are two-fold: to speed the development and testing of a new agent, and if it is active, to assure that the public has unencumbered access to the drug, at the earliest possible time. Further, NCI has followed a strategy of trying to promote the development of competition that we hope will benefit the consumer. We have followed this strategy in our development of both cancer and AIDS drugs, as I will describe further.

Taxol

Taxol® is a promising new therapy derived from the bark of the Pacific yew tree, that has proven effective for many thousands of patients with ovarian cancer and breast cancer. The development of Taxol® provides a model for technology transfer. Its continued development is a very high priority for NCI. Following its discovery and initial clinical trials, its production presented a formidable obstacle; only gram quantities, enough to test in a few hundred patients per year, were produced by NCI in the early years of its experimental development. The first promising signs of antitumor activity were reported in 1989, but further development and marketing required an industrial partner. NCI could not offer market exclusivity, because the drug had not been patented by NIH. However, the FTTA did allow the negotiation of a Cooperative Research and Development Agreement (CRADA), in which we offered our clinical trials support and our clinical data to a partner in return for a commitment to produce the drug and bring it to market.

In 1991 NCI entered into a CRADA with Bristol-Myers Squibb (BMS) for the further development of Taxol®. This offer followed a full and open competition and a thorough scientific review by government scientists of the four proposals received in response to our solicitation. BMS was chosen after careful deliberations by an expert panel of NCI scientists, and in January of 1991 agreed to terms with NCI.

In seeking our CRADA partner, we asked that, in exchange for exclusive access to our data for purposes of obtaining FDA approval, our partner would be obliged to produce the drug in amounts required for research and development; cooperate with us in executing a broad research agenda; assure access for all patients needing the drug; and set a fair market price. However, the CRADA provided no specific guidance on how a fair price would be reviewed by NCI. Taxol® represents the second instance in which a new drug, developed by the government, was subject to a price clause. The first instance was ddI, which I will discussed further in the context of AIDS drug development.

The Taxol® CRADA explicitly acknowledged the need to establish a fair and reasonable price, and states that BMS should consider the public investment in the drug's research and development and the health and safety needs of the public in setting its price. The CRADA also recognized that Taxol® is not patented, and that NCI is free to collaborate with other companies in the development of Taxol® analogues, some of which conceivably might be more effective and less toxic than Taxol® itself. Approximately one year ago, NCI entered into a CRADA with Rhone Poulenc to develop the Taxol® analogue Taxotere. This strategy of fostering competition is central to NCI's technology transfer program. We expect that Taxotere will be a direct competitor with Taxol® and will, through the usual market forces, further reduce the price of Taxol®. In addition, it is possible that other drug firms can complete with BMS in marketing Taxol® in the near future now that they have observed that Taxol® has been successfully brought to market. The development of Taxol® would not have been possible without the important contributions of a partner with substantial capability for natural product production and distribution. In fact, if Congress had not passed the FTTA, Taxol® would not be available to the women who need it today.

In implementing the fair-pricing clause, NCI considered several options. We could have attempted to conduct a detailed cost analysis of the proposed price, but rejected this alternative for several reasons. The Taxol® CRADA did not require the company to disclose proprietary information regarding total costs of production development and marketing, and, when asked to provide such data, the company exercised its right not to disclose such information. Even if we had obtained the information, NCI lacked the expertise in pharmaceutical price setting to conduct the necessary analysis. A number of intangible and unqualifiable factors contribute to a "fair" price, including the market life of the product, the period of market exclusivity, potential competition of related products, and anticipated market size, all of which defy precise delineation.

We believe that, despite the difficulties in its implementation, the pricing clause has been useful in controlling the price of Taxol®. It has made the pricing issue a matter of public interest; in so doing, it has undoubtedly exerted considerable pressure on the company to moderate its pricing strategy. Specifically, it has allowed the NCI to argue forcefully for a pricing strategy that provides total access to the drug, both for those who can afford it and those unable to pay. It has allowed us to guarantee that the thousands of patients already receiving Taxol® on a compassionate basis will continue to receive the drug free, even though Taxol® has been approved by the FDA.

AIDS Drugs

NCI has also played an important role in the development of several AIDS therapies, in close collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). During

the earliest work, federal laboratories did not have the many advantages conferred by the Federal Technology Transfer Act of 1986. I will return to this point later. NCI's involvement in AIDS therapy resulted from our early efforts to isolate the AIDS virus and to develop a blood test for AIDS infection. In addition, NCI's commitment to this area is a logical outgrowth of a longstanding commitment to develop drugs for cancer. Certain anti-cancer drugs and anti-AIDS drugs are in the same chemical class so that our cancer drug development experience was particularly relevant and useful. Our initial collaborations in AIDS drug discovery were undertaken as investigator-initiated research, and not as a major part of any extramural NCI program. The successful outcome of these early projects in identifying antiviral compounds such as AZT led to collaborations with the private sector and Duke University in the testing of AZT in 1985. The compound was entered quickly into phase I testing, and received marketing approval in 1987.

Also in 1987, NCI and NIAID established an agreement in which NCI would have responsibility for large-scale screening system of new agents for treating AIDS, and since that time has tested tens of thousands of compounds submitted for evaluation either from its own intramural research program, from academia, from private industry. This large scale screening effort is somewhat different from earlier investigator initiated research, in that a more automated and routine screening procedure had then been set in place. Also, and of great importance, in 1986 the Congress in its wisdom had passed the Federal Technology Transfer Act. Every federal research laboratory was given additional tools for the transfer and commercialization of federally developed technologies. Specifically, the FTTA permits Federal agencies to negotiate CRADAs with other agencies, private industry, state and local governments, and non-profit organizations. NCI researchers, in collaboration with other government scientists, undertook the preclinical and early clinical development of several new agents, and initiated their first clinical trials under NCI INDs. For example, these pilot trials defined the toxicity profiles of two new antiviral compounds, ddI and ddC, established their activity against HIV, and determined a variety of pharmacokinetic parameters important to understanding their action. In addition, the government provided drug for the initial clinical testing of these agents. Thus, the first drug licensed to industry as a result of these efforts was ddC, which was awarded to Hoffman-LaRoche in May of 1987 following a full and open competition. ddC was approved for combination therapy with AZT in 1992, after the completion of a series of clinical trials sponsored by the company and by NIAID and NCI.

In October of 1987, NCI licensed a second compound, ddI, to BMS, following a second open competition. BMS joined NIAID and NCI in conducting extensive clinical trials that confirmed early evidence of activity in patients who no longer responded to treatment with AZT. In addition to pursuing its usual activities as the drug licensee and sponsor, BMS played a noteworthy role in establishing a unique "compassionate" release program and a free

parallel track distribution process for patients ineligible for regular clinical trials. Approximately 20,000 patients received ddI in this parallel track program.

In negotiating the ddI license agreement, the government inserted a clause requiring the licensee, BMS, to charge a fair and reasonable market price. This clause was inserted in response to concerns of the public the Congress that the price of AZT may have been set too high, particularly in view of the contributions of the federal government in supporting the initial synthesis of AZT and discovering its anti-AIDS activity. It is important to note that NIH is, to our knowledge, the only federal agency to insert a reasonable pricing clause in its CRADAs and licenses. The purpose, if nothing else, is to put companies on notice that the government's contribution and consumer's interests must be taken into account. BMS, the ddI licensee, obtained FDA marketing approval in the spring of 1991 and set a price that was 20% of the entry price of AZT four years earlier. The company also established a broad program for free distribution of drug to indigent patients, a practice it has continued with Taxol®.

Both ddC and ddI have proven effective as alternatives to AZT for certain patients, and there is growing evidence of their value in combination with AZT. Because their toxicity profiles differ, and because the three drugs do not share cross-resistance, all are valuable therapies for the treatment of AIDS patients.

A number of new drugs are now under development in the NCI and NIAID systems. Some are compounds discovered and patented by NIH scientists, while others are being developed under collaborative agreements with industrial sponsors who own rights to the compounds. A number of therapies are being studied including protease inhibitors, 3TC (3'-thiacytidine), AGM-1740, TIBO-like compounds, tat inhibitor, and all-trans retinoic acid. In addition, a number of vaccines against AIDS are being studied. Two major considerations in establishing priorities for drug development are the uniqueness and the anti-AIDS potential of the candidates.

A number of question have been raised regarding the cooperation between government, academia, and industry in cancer and AIDS drug development. In a more general sense, the future of the American pharmaceutical and biotechnology industries depends on this cooperation. The remarkable discoveries now coming from federal and academic laboratories

-- the growth factors, the biological agents, and natural products that one reads about daily in the best academic journals -- can only reach the public through commercial partners. However, both academic and government laboratories must take seriously the intent of the Bayh-Dole Act, and that is to commercialize their discoveries for the benefit of the public. In their licensing agreements with large American and foreign firms, American academic institutions and federal laboratories must seek partners that will recognize the public's investment and the public's right to full and fair access to the products derived from that research. Commercial partners must be keenly sensitive to this intent, and must assure broad and fair access to these advances in technology and health care through responsible pricing strategies. And finally, companies must be willing and able to defend their pricing strategies in a public forum.

The CHAIRMAN. Thank you very much, sir; that was good timing.

Let me ask a question here, if I might. It seems that the pharmaceutical companies—and I don't want to use the word belittle—but it seems like they don't take much stock, sometimes, in the contributions of NIH. It seems like they sort of talk down about what NIH is actually doing. They say NIH doesn't patent any drugs; they say that almost all the new drug discoveries are coming from the private sector. They don't give much credit to NIH. Do you have a comment on that?

Dr. HEALY. Senator Pryor, one of the most frustrating things for us at NIH is that I don't think the American public understands how vital NIH is to their health and to their well-being. I think that some taking for granted for the contributions of NIH is a social disease in this country.

The CHAIRMAN. Well, I'm talking about the pharmaceutical industry.

Dr. HEALY. I think that they may reflect that. I think the pharmaceutical companies that work with us directly have a great sensitivity to the importance of NIH, not only in patenting and licensing, which is a small part of it, but in the training of scientists that NIH undertakes. Most of the scientists in industry that are doing research have in some fashion been trained by NIH, or done research in NIH funded institutions prior to going there.

So, I think it would be sad to stereotype the entire industry, but I don't believe that that attitude is unique to the pharmaceutical industry.

The CHAIRMAN. Good. I'm learning. This is a whole new area, a whole growth experience for me to learn about this. I hope we can take those stereotypes and put them aside, if in fact they are stereotypes.

I have here a list of 121 drugs now under development at NIH. Are we keeping track of the costs, the research costs, of the NIH and also of the contributions of the pharmaceutical manufacturers for each one of these trials? Are these clinical trials, or are these actual drugs developed by NIH?

Dr. HEALY. Mr. Chairman, it differs, depending upon the particular drug. In the case of AIDS and cancer drugs in particular, NIH plays an unusually active role at the level of drug development. In some cases we actually hold the patents and license. There our contribution to the actual development of the drug, the invention in itself, is more substantial.

In other cases, we might be participating in funding a clinical trial of a drug that was developed solely by industry, or a whole series of trials. In each case, we have the ability to go and come up with general estimates of the Government's contribution as it specifically relates to a given product. Obviously, we don't take into account the broader base of molecular and cell biology that underspins all of the research we do.

With regard to the numbers from the drug companies, of course, those we do not have access to.

The CHAIRMAN. You just stated that NIH does have certain patents and licenses. Do you have royalties that come back to the NIH in any form?

Dr. HEALY. In most of our CRADAs or licensing agreements we roughly get about 5 percent. That is a figure that we generally negotiate.

But the bigger issue is that only 11 percent of our entire research portfolio, roughly $1 billion, is conducted in a Federal laboratory, which would mean that we would hold the patent or be involved in licensing. More than 80 percent of the research that NIH does is in your State, and Senator Cohen's State, and is assigned to that institution. They deal with the patents. They get the royalties on any licensing arrangements.

The CHAIRMAN. You mean they are assigned to private enterprise, to pharmaceutical companies, or to universities?

Dr. HEALY. The universities. Under the Bayh-Dole Act of 1980, the Congress granted the rights to those inventions to the grantee institutions. NIH is out of the loop.

Prior to the Bayh-Dole Act the NIH had to be consulted, and had to approve when a university or research institution funded by NIH would enter into any kind of patenting or licensing agreement, or even apply for a patent, as a matter of fact. Under the Bayh-Dole Act, and so for the past almost 13 years, the NIH has been out of the loop on patenting and licensing of inventions made by grantee institutions. We have 1,600 institutions that we fund. We fund virtually all of the major research institutions in this country to do medical research, and they hold the patents; Harvard, Stanford, University of Wisconsin, the University of Michigan. They own those patents.

The CHAIRMAN. So NIH today receives no income from patents or licenses?

Dr. HEALY. We do only from the patents or licenses that we hold in our Federal laboratory, which is roughly 10 percent of our portfolio, such as drugs like ddI, where we hold the patent.

What I am saying is that 80 or 90 percent of the time we don't even have rights to the patents. If you say of all the university patents that have come out of NIH supported research, the bulk of them are not held by the Government. They are held by universities and research institutions under Bayh-Dole.

The CHAIRMAN. Has the Government given away too much of this to the universities or to the private sector?

Dr. HEALY. I think that the philosophy of Bayh-Dole was to promote better relationships and cooperative partnerships between industry and universities, to stimulate universities to aggressively pursue inventions, and see that they get commercialized. The concern was, back in the 1970's and 1980's, that too many of the basic discoveries were not being developed into commercial products, and that this was anticompetitive. It was the spirit of Bayh-Dole, which I know you all supported here, that we should encourage universities to participate in commercial activities in the best interest of the public.

From NIH's perspective we do not get money out of this. From NIH's perspective, our goal is to do science, not for science's sake, but to see that products come to market that help the American public who need them. So tech transfer is a crucial part of our mission.

The CHAIRMAN. Senator Cohen.

Senator COHEN. Thank you, Mr. Chairman.

As was indicated earlier this morning, this is a very serious issue and it is important that none of us, certainly on the Committee and none in the vast audience that we have here today, develop a mindset which says it is us against them.

I don't want to share the company of those who advocate that what we ought to do is have the Federal Government take over the manufacture of drugs in this country. I think it is important that we not kill the goose that is laying the golden medicinal egg.

But I want to assure those who represent the pharmaceutical industry who are here today that we would like that goose to experience some restraint in placing its gold. Perhaps if we could have silver, or brass, it would do the job, but we will not have to pay for the gold. That is the attitude I would like to see them continue.

I have been a major supporter of Senator Pryor's efforts to get some restraint on the pricing of drugs in this country.

I was interested, Dr. Healy, when you said that NIH took action, without any requirement to do so, to insert or insist upon a reasonable price clause, because you were outraged about the pricing of AZT.

What factors did you take into account in determining what a reasonable price was in those two drugs that have come to market, among the many agreements that you have?

Dr. HEALY. That went back several years. Back in 1979 that was really an outrage, both on the part of NIH, who felt that they played a crucial role in the development of AZT. In fact, NIH is currently involved in litigation surrounding that very drug and our belief that we have co-inventorship rights there. That led to the inclusion of the reasonable pricing clause.

The difficulty with the reasonable pricing clause is it was a spiritual statement. It was a statement of trust, of understanding that we thought that the companies should recognize the public investment, but in fact, if you look at the contractual agreement, there are no teeth. There is no mechanism at NIH for enforcing it. There is no contractual responsibility on the part of any of the partners to divulge information that would lead to a mechanism to achieve a price. There is no articulation of what pricing strategy might even be.

So we have been faced with the dilemma of asking for an agreement in concept and principle, as I said, sort of a spiritual agreement, but not having the ability to put the teeth in it. We do feel that if it were dealt with by some other agency outside of NIH, and we do believe that should be the case, then we could take the reasonable pricing clause out of the contract or move it up to the preamble and just say we understand that the public investment should be taken into account.

Senator COHEN. When you say it is a spiritual thing, or a spiritual provision, it is really a meaningless provision, is it not?

Dr. HEALY. I think spiritual things are very meaningful, but they aren't necessarily things you can put your arms around and act on and implement. I think that we believe at NIH that the statement that the public should have a return on its investment is an important thing to articulate in those relationships, even if we don't have the ability to function as a regulatory agency and even if we don't

have the ability to put together the teams of economists and lawyers to figure out a price.

Senator COHEN. Let me not engage in any kind of teleological argument with you about the value of spirit in our lives. Let me suggest to you that when the Government undertakes to put provisions in a contract which give the appearance that we are concerned and that we are going to insist upon "reasonable prices," when in fact we have no expertise, no basis, no ability to determine what a reasonable price is. We have no way to monitor what a reasonable price is and no mechanism to enforce it. We are doing a greater disservice than by not having a clause in any event, because we are giving the appearance that we are doing something in fact, when we are doing nothing. That is why I said it is a meaningless phrase, or provision, in a contract, because there is no way in the world to either set it, monitor it, or enforce it.

I don't want to diminish the importance of spirit in our lives or spiritualism in our lives, but I think that does a greater disservice than nothing at all. That is why I was curious about what factors NIH would take into account. Would you take into account the costs of drugs already on the market? Would you take into account the cost of the private company to test, produce, and market that particular drug? Would take into account the future profits? None of that, none of that was considered.

My understanding is, from the testimony that has been presented and your written remarks, that the only thing that was done was that there was a hearing in which patients' groups were allowed to voice objections, and none did. No other effort was made to determine what a reasonable price would be. Am I wrong in that?

Dr. HEALY. I think that you are diminishing the efforts on the part of the NIH to deal with it.

Senator COHEN. Tell me what efforts you have made.

Dr. HEALY. First of all, there have been only two drugs that have come to market with the reasonable pricing clause, because there is a long time from the point at which you start investing in a CRADA and the point at which the drug actually comes out and ready for market and to be priced. We are learning as we go along.

The National Cancer Institute and Mr. Reid Adler, who have dealt with the pricing issues, have struggled with exactly how we can put teeth into the reasonable pricing clause. We have looked at things like the price of other drugs that have been on the market where we have not been able to get information, or proprietary information concerning the individual company.

But before I ask my colleagues to give you the details on the types of negotiations that went on with the company, I would just like to say that it should be noted that the Federal Tech Transfer Act of 1986, which encouraged, indeed mandated, the agencies like NIH to involve themselves, never mentioned reasonable pricing, never mentioned the spiritual concept of return on public investment. At least they did in a general way. In fact, the law said that.

If you read the Bayh-Dole, if you read the Federal Tech Transfer Act, there are a lot of statements of the spirit there about the public return on investment, about stimulating fairness, competitiveness, U.S. industry, but there is no way to technically enforce it.

That is why the laws are there. We felt that reasonable pricing, access to indigent patients, and compassionate use, were elements of the public trust that we felt we entered into when we negotiated a CRADA with a company.

Now, I would like to ask either Dr. Chabner or Mr. Adler to give you some of the detailed efforts that they went through, which were by no means trivial, to try to come up with pricing information.

Senator COHEN. Let me just comment, in view of what you just said, lawyers understand the word, it is called precatory—precatory language. We hope, and we are drafting wills now where we tell the people that we are leaving things to, that we hope you will do the following. We are not insisting upon it, we are not directing it, we hope you will live by the spirit of this wish. It seems to me that is what you have testified to today.

I'll be happy to hear from Mr. Adler and Dr. Chabner about exactly the kind of efforts you have made to make a determination of what a reasonable price is on any of these drugs.

Dr. CHABNER. There are really two drugs involved here. The first was ddI. It was the first that came to market under a fair pricing clause in its licensing agreement. The price for ddI was set at about 30 percent of the entry to AZT. At the time this price was set, the only test that was used was comparison with the price of AZT.

Senator COHEN. Which was too high.

Dr. CHABNER. Which was much too high.

It was generally acclaimed that this was a very reasonable price, and there was very little negative comment about the price at the time.

Senator COHEN. How would you know if there was negative comment? How much information do you have about the pricing of any drug? You don't know.

Dr. CHABNER. We hear from the same sources that I think you hear from. That is the public.

Senator COHEN. You don't get any information. We don't get information. I was at a hearing a couple of years ago when Senator Pryor asked the manufacturers to come before us and meet in private and discuss the pricing mechanisms. They are legitimately concerned about loss of proprietary rights, and secrets, and so forth. We didn't get any information out of them. I doubt very much whether anybody else does either.

So you tell me, what information are you relying upon?

Dr. CHABNER. Information for what, Senator?

Senator COHEN. For the pricing. What is reasonable and what is unreasonable?

Dr. CHABNER. The only information we relied on is a comparison with currently marketed products of the same type. In fact that is the test that Canada uses in setting its prices.

Senator COHEN. They start at a much lower level, don't they?

Dr. CHABNER. Not for all prices. For example, Taxol is priced higher in Canada than in the United States.

Senator COHEN. Can you give us a breakdown in terms of the comparison? Do you have such a list?

Dr. CHABNER. I don't have a list. Actually, I think GAO has done a study of that recently. Many of the products sold overseas are lower, that is true. Of the few that we are talking about, ddI is priced the same or higher overseas; and Taxol, which was the other product marketed under a fair pricing agreement, is priced lower in the United States.

Senator COHEN. We hope to get a breakdown on the rough comparison. What you are saying is that you just draw upon what is out on the marketplace, or what is in the Canadian marketplace, or what is in the European marketplace?

Dr. CHABNER. In the case of Taxol, the way we approached it—because we asked for proprietary information about cost of production, and we could not get it—the only option we felt we had at that point was to look at the comparison of products currently being marketed for the same indication, and other cancer drugs. The list that was shown earlier is actually the list of drugs marketed for cancer in the last 3 years. That was the basis for comparison.

Taxol is a much more expensive drug to produce than many of the other drugs on that list. So we felt we had some feel for it. We had been in the business of producing Taxol. On the actual price, what we asked the company to do was to come in with a price that was below the median for drugs marketed for the same general class, and comparable to other drugs marketed for the same indication, which was ovarian cancer. They satisfied both of those stipulations.

Senator COHEN. Dr. Chabner, how much was spent by the Government in developing AZT, or by the Cancer Institute?

Dr. CHABNER. I really don't have the figures. I think it was something like $10 or $11 million, but I can't give you exact figures.

Senator COHEN. Can you provide that for the record?

Dr. CHABNER. Yes, we can.

Senator COHEN. Dr. Healy, let me ask you whether there is any benefit in these CRADA agreements as far as does it expedite—let me backtrack a moment.

After a drug company enters into a CRADA agreement in which a drug is then designed, developed, whatever—you have to go to FDA to get approval, right?—is there any benefit to a pharmaceutical manufacturer in having a CRADA agreement in terms of expediting the process with FDA? In other words, does it give them a benefit of having a stamp of approval, of having it developed, co-developed, or some arrangement with NIH so you have a Good-Housekeeping stamp of approval, or is there no difference?

Mr. HODEL. We are the ones who enter into these CRADAs. The way we approach them is that they have to be based on a piece of research that NIH thinks is important to its mission to have done. Second, there has to be some intellectual contribution on the part of the industrial partner. It cannot just be that they are dumping money into a lab and hoping that a patentable product comes out. So that we expect them to bring some intellectual expertise to the table in addition to resources, which sometimes includes money, and sometimes includes individuals.

You can argue that when research has been conducted by the NIH, whether it is under a CRADA or whether it is in our grantee

institutions done by Harvard or the University of Michigan or Yale, that there is a certain stature associated with it, because it is done by a distinguished institution. But I think that it does not have any specific role with regard to who we deal with as a partner. I mean we are interested in the research and the substance of the research.

Senator COHEN. That is not what I was asking. I was asking whether or not it is a benefit to any of the manufacturers to have this arrangement with NIH. Does it help expedite?

Dr. HEALY. Certainly. Yes, because basically they are in a research partnership, and hopefully the purpose of the research partnership is to get the work done better, faster, more effectively.

Senator COHEN. Dr. Arno testified on the last panel. He estimates that between 1987 and 1992, AZT generated about $1.4 billion in revenues for Burroughs Wellcome. Do you have any information on that?

Dr. HEALY. I don't have information about that number, but NIH has been deeply concerned about the very high cost of AZT. As you probably know, about a year and a half ago we entered into a licensing agreement for AZT with another company besides Burroughs Wellcome, with the express intent of stimulating competition to try to bring down the price of that drug, because we think it was too high.

Senator COHEN. Does the current cost of treating an AIDS victim of about $3,000 a year, which we got from one of these charts here, does that reflect the cost of developing that drug?

Dr. HEALY. I don't have any way of knowing that.

Senator COHEN. Dr. Chabner.

Dr. CHABNER. We really don't know.

Senator COHEN. That is all I have. Thank you.

The CHAIRMAN. Did your second contract, or second supplier, let's say, of AZT bring down the cost of this drug?

Dr. HEALY. Unfortunately, it is involved in litigation right now. I suspect the cost of litigation, just based on the depositions that NIH has been put through, are probably going to be so excessive that by the time it is reflected in the cost, it is hard to imagine that it might not even go up.

But until that is litigated, and until it is determined whether or not NIH can establish co-inventorship rights—Burroughs Wellcome is challenging the fact, saying that we do not have co-inventorship rights—we won't know whether or not multiple licensing can be granted, and the price will go down further.

The CHAIRMAN. I'm unclear about something, Dr. Healy. Before Burroughs Wellcome walked out the door with AZT and the rights to sell $1.4 billion of AZT in 5 years, were they asked how much they were going to charge for this?

Dr. HEALY. AZT, of course, was developed prior to the time that NIH had CRADA's, before the time NIH had an aggressive program of seeking patents on its own inventions. NIH believes that it is a co-inventor of AZT.

Burroughs Wellcome, however, had the orphan drug rights to the drug. They did not acknowledge NIH's inventorship rights, and consequently, they marketed at whatever price they chose. There was no reasonable pricing clause. There were really no terms of

agreement that would have us even have a comment on the price. That came out at an extremely high price. The community was enraged. NIH was enraged. The Department was enraged. That led to our reasonable pricing clause.

Subsequent to that, a small pharmaceutical company came to the NIH and said, if you believe you are co-inventors, we would like you to license the rights of AZT to us. In other words, there would not be an exclusive license. We did so, and that precipitated a lawsuit on the part of Burroughs Wellcome against that company and against the NIH, in essence because they are disputing NIH's claims to co-inventorship rights.

Senator COHEN. Do you have negotiating capacities at NIH? I know you have wonderful research capacities in health, but do you have negotiating capacities with the pharmaceutical manufacturers?

Dr. HEALY. We have an Office of Technology Transfer, which is ably headed by Mr. Reid Adler. We also have lawyers that come to us from the Department. We also have an Office of General Counsel. We do not have our own independent legal staff. Both of those offices, the Office of General Counsel from the Department of HHS, and our Office of Technology Transfer, deal with most of these issues.

We do not believe we have the resources, nor do we want them, to do price regulation. These are nonregulatory lawyers. These are lawyers who deal with contracts that are at a research level.

The CHAIRMAN. I know you don't want to be in the pricing business. I understand that, but shouldn't you consider it a factor in dealing with which company walks out the door with the rights to sell, and at huge profits, some of these drugs? Shouldn't it be a factor as to what they are going to charge the general public.

Dr. HEALY. I absolutely agree with that. I think that, at the risk of seeming difficult, I think that the spirit of the tech transfer laws that have governed our agency listed several things. They listed U.S. industries being given preference; they listed small businesses being given preference; they listed access to the American public being given preference; they listed the whole notion of a return on investment to the American taxpayer. One thing that they left out was the whole issue of the price of those discoveries once they actually hit the marketplace.

The CHAIRMAN. Do you want us to write that into law?

Dr. HEALY. I think that is something for you to consider. Obviously, you are considering it.

The CHAIRMAN. Senator Cohen, do you have any further questions?

Senator COHEN. No. The only point I was going to make once again, is that I don't think we ought to talk in terms of spirit when it comes to enforcement of contract, and in terms of pricing arrangements. The notion that somehow we are going to call upon the private sector to abide a notion as ephemeral and vague as the spirit of the contract I think is not a healthy thing.

Dr. HEALY. But I think we agree. All I am saying is that we don't have the statutory authority to do more. We do what we can. We have done more than any other agency within the Federal Government to recognize this is a problem and try to deal with it.

Senator COHEN. All I am suggesting to you is that by recognizing it and trying to deal with it, the fact is you have already stated in your written testimony, you don't have the means or the expertise for the enforcement or anything else.

Dr. HEALY. Right. We don't have the authority. We are an agent of the law.

The CHAIRMAN. If you don't have the authority, have you ever asked for the authority?

Dr. HEALY. We have never asked for the authority to be a price regulator. I don't think we will.

Dr. CHABNER. Senator Pryor, I'd like to comment on when a price should be set. I think that is a very important issue. We heard comments earlier today that it should be set at the time that a license is offered. That ought to be part of the licensing process. That will work where you know what the indications are for the drug, and whether the drug is going to go to market very soon. That is sometimes the situation. We have a product with a very well-defined use, a well-defined market, and a company really estimates what it is going to cost to produce it.

In the case of Taxol, when the agreement was signed in 1991, the potential market for that drug was very small. It was a very difficult molecule to produce. The company, really, at that point did not know how they were going to make it when they accepted the license. They thought they would probably have to use the natural resources, the bark. In fact, what has happened is that there has been a transition. The market has also changed in size.

It would be very difficult to get a product price from a company when a drug is at that stage. I think it would be much more effective to get the price at the time of marketing for some drugs. So you have to be flexible about that.

Senator COHEN. What would you have to take into account? You can negotiate contracts that take into account the difficulty of bringing a certain type of drug, just like we deal with in other facets of the Federal Government. We negotiate costs-plus contracts. We have set contracts. We provide for incentives for contractors to come in under a particular price. That can be negotiated, depending upon the difficulty and the complexity of the issue involved. You don't have to set an ante up front. You can have escalator clauses. We have problems with people who buy into contracts at a low price, and as soon as the product is approved they say, "By the way, we have these changes we have to make."

Dr. CHABNER. You are proposing something that is much more complex than we had.

Senator COHEN. It is a complex issue. That is why we are holding the hearings.

Dr. CHABNER. The other factor that I think is very important to consider is that one of our major concerns is to get the product to the public quickly. These are lifesaving drugs, and you have to choose a licensing system not only that offers you a low price, but somebody that has the capacity to really produce it and get it to market. That is not a trivial problem.

We have licenses now which are stuck with companies that don't have the wherewithal to get them to the public. The fact that you have chosen a good company is a very important aspect of this, to

choose the right company to do the job. I am sure that is the same in producing aircraft, or whatever it is. When you are dealing with life-threatening diseases, it is an overriding consideration.

The CHAIRMAN. We want to thank this panel. We thank all of you for attending. We look forward to working with you in the future.

We are going to call our final panel now. Mr. Gerald Mossinghoff, the president of the Pharmaceutical Manufacturers Association; and Mr. George B. Rathmann, Ph.D., of the ICOS Corporation of Seattle, Washington. We welcome both of you here this morning.

Mr. Mossinghoff is certainly no stranger to our committee. We welcome you back to our committee, Mr. Mossinghoff, and also you, Mr. Rathmann.

Mr. Mossinghoff, if you'd like to, you can lead off.

STATEMENT OF GERALD J. MOSSINGHOFF, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. MOSSINGHOFF. Thank you, Mr. Chairman. I appreciate once again the opportunity to testify before this Committee.

As the Committee knows, over 90 percent of new medicines are brought into use in the United States, or discovered, invented, tested, developed, and produced by America's pharmaceutical industry. However, from time to time important new therapeutic approaches are discovered by NIH scientists, as has been amply testified to today, under NIH grants, or through collaborative efforts by private sector scientists.

For many years now the NIH has encouraged the research, development, and eventual marketing of promising new therapies, first discovered in research sponsored by NIH, by relying on the cooperation and proven capabilities of research-based pharmaceutical companies. In the Bayh-Dole Act of 1980 and again in the Federal Technology Transfer Act of 1986, Congress reaffirmed its reliance by authorizing exclusive patent license agreements with the private sector and by authorizing Federal entities to enter into CRADAs with industrial organizations.

The 1986 act recognizes that exclusivity is a powerful incentive to the private investment necessary to bring the results of governmental research to patients in the form of new medicines. PMA believes that in general the 1986 act is working well, as are the licensing and contractual policies consistent with that act and the Bayh-Dole Act.

As NIH officials have stated, Government agencies and laboratories have neither the capability nor the expertise to undertake and manage the massive clinical trials and other work necessary to develop and obtain approval for new drugs, and after approval, to produce, market, and distribute in commercial quantities final dosage forms to patients.

The goal of Government licensing and research policies obviously must be to encourage the participation of private entities if discoveries that sometimes emerge from that research are to become new therapies useful for patients. If these policies fail for whatever reason to achieve this goal, potential therapies will languish and will not be commercialized as quickly as possible or perhaps may never be widely available to treat diseases.

NIH has stated that it does not have price assessment capabilities. As we do not believe the NIH should be in the price regulation business, we would oppose the establishment of additional pricing capabilities within the NIH. The overriding Government goal should be to encourage companies to enter into cooperative arrangements so that promising new compounds will be developed for patients.

This objective could clearly be compromised if the Government becomes more involved in reviewing, second-guessing, or challenging a company's pricing determinations for individual products. Additional Government involvement in pricing would not only be unwise public policy, but also, we believe, a misuse of limited NIH resources. Pricing decisions are far more complex than simply reviewing development cost data, itself a complex task. We view the creation of an NIH panel or other mechanisms as inappropriate, and perhaps even counterproductive.

There are several additional points that should be noted by the Committee in assessing the licensing policies of NIH. First, the terms of an exclusive license are to fairly reflect the relative contributions of the parties to the invention and the CRADA; the risks incurred by the collaborator; and the cost of subsequent research and development needed to bring the invention to the marketplace.

Royalty-bearing licenses are contemplated, with royalty rates based on product sales. We understand that some NIH licenses require royalty payments to the Government in those instances where the compound under development and its patent is protected.

Second, NIH has control over which company is selected as a CRADA partner. There is no obligation that NIH enter into a CRADA or patent license with a company about which it has any appropriate concern.

Third, NIH may contractually terminate an arrangement if a company breaches its contractual obligations, including those relating to pricing.

Finally, the best possible means of ensuring broad access to new therapies and fair and responsible pricing is to promote competition in the marketplace. NIH is already pursuing such a strategy by entering into the CRADAs involving potentially competitive products developed by different companies.

Mr. Chairman, this concludes my brief summary.

[The prepared statement of Mr. Mossinghoff follows:]

Statement

Pharmaceutical Manufacturers Association

GERALD J. MOSSINGHOFF
PRESIDENT
PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

SPECIAL COMMITTEE ON AGING

UNITED STATES SENATE

FEBRUARY 24, 1993

Mr. Chairman and members of the Committee:

I am Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association. PMA represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription drugs used in the United States, and a substantial portion of the medicines used abroad. I appreciate the opportunity to appear before the Committee today to present the industry's views on cooperative Government-industry drug development efforts and specifically on Cooperative Research and Development Agreements (CRADAs) between PMA member companies and the National Institutes of Health (NIH).

As the Committee knows, over 90% of new medicines brought into use in the United States are discovered, tested, developed and produced by the pharmaceutical industry. However, from time-to-time important new therapeutic approaches are discovered by NIH scientists, under NIH grants, or through collaborative efforts with private sector scientists. For many years now, the NIH has encouraged the research, development and eventual marketing of promising new therapies first discovered in research sponsored by NIH by relying on the cooperation and proven capabilities of research-based pharmaceutical companies. In the Bayh-Dole Act of 1980, and again in the Federal Technology Transfer Act of 1986, Congress reaffirmed this reliance by authorizing exclusive patent license agreements with the private sector and by authorizing federal entities to enter into CRADAs with industrial organizations.

The 1986 Act recognizes that exclusivity is a powerful incentive to the private investment necessary to bring the results of governmental research to patients in the form of new medicines. PMA believes that in general the 1986 Act is working well, as are NIH's licensing and contractual policies consistent with that Act and the Bayh-Dole Act.

CRADAs generally focus on early research activities such as screening compounds, developing receptor technology and conducting other basic research drug-discovery activities. At this early stage, Government and corporate researchers can collaborate to identify and pursue research leads. Normally it is not the role -- or even within the capability -- of the Government to develop into a marketable product a compound that results from this collaboration. This development activity includes toxicology and carcinogenic testing, drug substance stability and formulation testing, and clinical trials, followed by extensive interaction with the Food and Drug Administration. These activities typically are the responsibility of the corporate "partner". Under NIH policy, the Government is usually compensated for its role in the early research of the patented drug by a royalty. The amount of the negotiated royalty is based upon a number of factors including the degree of risk assumed by the corporate partner. Obviously, the risk of failure in completing all the necessary steps following discovery of a potential new therapeutic is very high.

As NIH officials have stated, Government agencies and laboratories have neither the capability nor the expertise to undertake and manage the massive clinical trials and other work necessary to develop and obtain approval for new drugs and, after approval, to produce, market and distribute commercial quantities of final dosage-form products to patients.

The goal of Government licensing and research policies obviously must be to encourage the participation of private entities if discoveries that sometime emerge from that research are to become new therapies for patients. If these policies fail, for whatever reason, to achieve this goal, potential therapies will languish and will not be commercialized as quickly as possible or perhaps may never be made widely available to treat disease.

The 1986 law authorizing CRADAs makes no reference to inclusion of pricing provisions in such agreements. In practice, Federal agencies, other than NIH, have chosen not to include a pricing clause in their agreements. NIH as a matter of contract has elected to include a pricing provision in its CRADAs and in individual patent license agreements. The model pricing provision developed by NIH for CRADAs is properly phrased in somewhat general terms. Under it, NIH may require the CRADA partner to support by reasonable evidence the relationship between the pricing of the licensed product, the public investment in that product and the health and safety needs of the public. This does not permit NIH to set or dictate prices for licensed products. This general provision allows both NIH and the CRADA partner to negotiate regarding pricing information, if that is their mutual desire, based on the circumstances of the particular product in development.

NIH has stated that it does not have price assessment capabilities. As we do not believe NIH should be in the price regulation business, we would oppose the establishment of additional price assessment capabilities within NIH. The overriding Government goal should be to encourage companies to enter into cooperative agreements so promising new compounds will be developed for patients. This objective could clearly be compromised if the Government becomes more involved in reviewing, second-guessing or challenging a company's pricing determinations for individual products. Additional Government involvement in pricing would not only be unwise public policy but also a misuse of limited NIH resources. Pricing decisions are far more complex than simply reviewing development cost data -- itself a complex task -- and we view creation of an NIH panel or other mechanism as inappropriate and, indeed, counterproductive.

PMA does not become involved in individual company determinations to enter into CRADAs or company negotiations with a Government agency regarding the development and commercialization of any compound. Several PMA companies are CRADA collaborators. NIH representatives have testified that other research-based companies have declined to enter into CRADAs because of concerns over pricing clauses. Successful companies are not limited in their future R&D investment choices to a single project or family of therapies. A particular company, in determining how best to invest its research and development dollars, may well choose to put its resources into projects that do not

raise the probability of Government access to internal pricing information and protracted public proceedings about pricing decisions.

There are several additional points that should be noted by the Committee in assessing NIH licensing policies. First, the terms of an exclusive license are to fairly reflect the relative contributions of the Parties to the invention and the CRADA, the risks incurred by the Collaborator and the costs of subsequent research and development needed to bring the invention to the marketplace. Royalty-bearing licenses are contemplated with royalty rates based on product sales. We understand that some NIH licenses require royalty payments to the Government in those instances where the compound under development is patent protected.

Second, NIH has control over which company is selected as a CRADA partner. There is no obligation that NIH enter into a CRADA or patent license with a company about which NIH has any appropriate concern. Third, NIH may contractually terminate an arrangement if a company breaches its contractual obligations, including those relating to pricing.

Finally, the best possible means of ensuring broad access to new therapies and fair and responsible pricing is to promote competition in the marketplace. NIH is already pursuing such a strategy by entering into CRADAs involving potentially competitive products developed by different companies.

The Chairman's invitation to testify at today's hearing requests that PMA address five questions of particular concern to the Committee. We offer the following responses.

How does federal government research on new drugs reduce the R&D risk for pharmaceutical manufacturers?

The Federal Government's activities in the areas of both basic research and targeted drug discovery, such as screening of compounds for possible therapeutic application, do not reduce to any significant extent the company's risks in developing that compound into a new and therapeutically useful pharmaceutical product. Generally, the company becomes involved at a very early stage in the overall

research and development process and therefore confronts approximately the same R&D risks as it would were all the initial research done in the private sector.

Does the industry believe that the federal government's involvement in new drug development should be reflected in some pricing benefit to the consumers?

The contractual agreement between the Government and its industry partner should mutually reflect the contribution of each partner to the agreement. This can be accomplished by either a negotiated royalty arrangement based on sales of the later approved product if the federal partner has obtained a patent, or a pricing clause, if such a clause is mutually acceptable. Either arrangement will result in benefits to the Government and to U.S. patients if a safe and therapeutically effective pharmaceutical product ultimately results from the collaboration.

Does the industry support an arrangement with the government where a "royalty" is paid to the government, or one in which a price is negotiated up front for a CRADA drug?

It has been documented by NIH officials that the Institutes' requirement for a pricing provision has caused individual companies to decline to enter into cooperative arrangements for the development of potential new drugs. A particular company, in determining how best to invest its R&D dollars, may well choose to concentrate its resources on projects that minimize the possibility of Government access to internal pricing information. In our view, where there is a patent involved, serious consideration should be given to use of a contractual requirement under which the private partner returns a patent royalty to the Government based on sales of the product -- the usual arrangement if both the collaborators are in the private sector. In PMA's response to the Administration's Healthcare Transition Team, we noted that PMA would be willing to work with NIH to identify incentives for CRADAs and develop appropriate principles or models for compensation of Government contributions.

How can we assure that all types of federally-developed drugs -- that is those with lucrative markets, and those with smaller markets -- are commercialized?

There can never be an "assurance" that any promising compound discovered in either a company laboratory or a governmental facility will in fact become a pharmaceutical product due to the risks inherent in new drug development. We believe that an exclusive rights arrangement mutually negotiated between the Federal entity that discovered the new compound and the private company that commits its extensive development expertise is the only viable approach. Congress has repeatedly determined that exclusivity must be given to attract private funds to the development process with respect to Government inventions. Otherwise, potential therapies may not be commercialized as quickly as possible or perhaps may not be available to treat disease. Further, we question the premise upon which the Committee's inquiry is based -- that it is somehow possible to assess with any precision the commercial success or "market" for a new compound in the early stages of the development process.

How can we be sure that sufficient incentives exist for cooperative ventures between industry and the government, while assuring that drugs developed through these ventures are priced fairly?

In general, the current positions of the National Institutes of Health, as reflected in the model CRADA and model exclusive license arrangement, seen to include sufficient incentives for continued cooperation between industry and the Government to develop fairly priced new products, although as has been indicated several companies are reported to have declined to enter arrangements. The overriding policy objective must be to make available to patients, as quickly as possible, promising compounds resulting from Government research.

Mr. Chairman, this concludes my prepared testimony. I welcome any questions you or any other members of the Committee may have.

The CHAIRMAN. Mr. Mossinghoff, thanks very much for your statement. We will have a couple of questions to follow on.

Dr. Rathmann, I apologize to you, you are also no stranger to this Committee. In fact, I recall you came to the Committee in 1989. We appreciated your statement then, as we will appreciate your statement today, I am sure.

STATEMENT OF GEORGE B. RATHMANN, ICOS CORP., INDUSTRIAL BIOTECHNOLOGY ASSOCIATION, AND ASSOCIATION OF BIOTECHNOLOGY COMPANIES, SEATTLE, WA

Mr. RATHMANN. I am here on behalf of the Association of the Biotechnology Companies, and the Industrial Biotechnology Association, of which I have been a board member for over 10 years.

My submitted testimony documents the R&D intensive nature of this industry. It is the most R&D intensive industry in the country. It has been so documented many times, with perhaps about 38 percent of all expenses going to R&D in that industry.

I am presently chairman and chief executive officer of ICOS. I was the founder 13 years ago of Amgen, and remain as chairman emeritus.

When I testified several years ago, as you mentioned, we were here to try to assure you that the biotech industry was interested in cooperation, and did share some of the concerns that were expressed at that time. We still are here to help cooperate and bring information whenever possible.

Here in this session today a number of subjects have come up. I'd like to elaborate on some of those, because I think it might be helpful.

One of the reasons we felt we could be helpful was that biotech was an open book. We are public companies with limited products, and therefore our data would document the costs of many of the things that we were doing, nailed right down to the specific research programs. We felt it would serve the public and the congressional, and the industry, interests in order to share that information.

We pointed out at the time, for example, that we had raised $300 million and had yet to make a penny of profit at Amgen. We had done that with private investment. There was no Government investment involved in that. We felt that it was clear that this was a high-risk business and needed investment from investors that had confidence that ultimately we would be able to make a profit. Amgen has done that.

We did, however, at that time project pricing on our two main products that would be well below world prices. That has turned out to be true. Erythropoietin is priced as low in the United States as anywhere in the world, lower than Europe, and less than half the price in Japan. G–CSF, the second major product of Amgen, is priced under one-third of the amount at which it is priced in Japan, despite the fact that in Japan the government sets the prices. It is certainly measure of fair pricing.

We projected that these products would be cost-effective, and they have been. We projected that Erythropoietin would eliminate many blood transfusions, and in fact, over 1 million transfusions have been avoided since the introduction of Erythropoietin in just

this country alone. With the introduction of the second product, we projected the side-effects of chemotherapy would be minimized, and that has been true. In fact, for both of these products, there is good justification that they are cost-effective.

Many biotechnology products—I think this is an important perspective that this Committee should understand—Alpha-interferon and hepatitis-B vaccine, the development of hepatitis-C reagents, none of the major products of biotechnology have been involved in CRADAs to the best of my knowledge. That includes tissue plasminogen activator, EPO; G–CSF; and so on.

In most cases, we picked up these ideas at the very earliest stages. They were ideas that had been funded in part by NIH since, as Dr. Healy has said, more than 80 percent of the funding is at institutions around the country. The most important function of NIH—and I think Congress should be very proud of what they have done there—is the role that it has played in educating the people who are the structure of the biotechnology industry today, and in fact are the infrastructure that makes this country the leader in the world.

We feel that the emphasis on the CRADAs, which are only a small part of what NIH does, might fail to reflect the great importance that NIH has for the scientific infrastructure in the country, particularly the whole biotechnology industry and the foundation under it.

What kind of science transfer did we do in the biotech industry? What we did was to look at the basic science going on in these institutions around the country. In many cases we even supported some of that work ourselves, and translated some of that basic science into products. That basic science was available to all the companies in the world. It was published information in most cases. It is just a very fortunate thing that U.S. companies in the form of the biotechnology industry were able to translate that science into the products we are talking about.

I think it is a very different story than what we are hearing a lot about today with respect to products in which the NIH has taken a very important role, particularly cancer and AIDS. But the products we are talking about were basically the translation by technology transfer from the science that was generated in the institutions that the NIH was funding around the country.

In some cases these are royalty-bearing. In one case with one of the products, Sloan-Kettering has received more than $50 million from Amgen in return for the rights that were received from what was originally an NIH-funded program.

Today at ICOS we already are funding programs in basic science at the level of almost $1 million a year. We do not direct these people to do their science in such a way that will lead to products. Very little of this work is product-driven. It is really basic and knowledge-driven. That is the foundation of the industry.

We would try to assure you that the United States will continue to lead this industry in the future. I think you will see that the pricing has been responsible all along the way.

Thank you.

[The prepared statement of Mr. Rathmann follows:]

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STATEMENT OF GEORGE RATHMANN,

CHAIRMAN, PRESIDENT, AND CEO OF ICOS CORPORATION,

ON BEHALF OF

THE INDUSTRIAL BIOTECHNOLOGY ASSOCIATION

AND

THE ASSOCIATION OF BIOTECHNOLOGY COMPANIES

EXECUTIVE SUMMARY

Unlike established pharmaceutical companies, most biotechnology companies do not currently have products on the market and, therefore, cannot fund research and development from sales proceeds. Instead, at least 90% of the $4.9 billion spent by the biotechnology industry on R&D came directly from investors, including middle class investors participating through mutual funds and pension funds. And since biopharmaceuticals typically take 10 to 12 years to reach the marketplace, most biotechnology companies must seek successive rounds of public financing in order to secure the funding necessary to conduct R&D and build manufacturing facilities.

Investors take large risks with our companies. Substantial scientific, manufacturing, and regulatory hurdles must be overcome before a new product can be marketed. Experimental therapies fall by the wayside, sometimes accompanied by their corporate sponsors. The cost of failure is compounded by the extremely high level of investment required, as well as the time between drug discovery and marketing. Very few firms have achieved profitability, while a substantial number have either folded, merged, or been taken over. In light of this already risky investment environment, the continuing capital needs of biotechnology companies can only be met if investors can foresee a return commensurate with the risks, costs, and time involved in new biotechnology product development.

The riskiness of investing in biotechnology companies was again illustrated on Monday of this week, when disappointing clinical trial results led to a 67% drop in one company's stock price in a single day. If the market is a tough place for pharmaceutical companies these days, it is even tougher for biotechnology companies. Our reliance on declining equity investments in the pharmaceutical industry is already threatening the viability of ongoing research programs.

The biotechnology industry cannot responsibly ignore the concerns raised by this Committee and others about pharmaceutical pricing. But in crafting solutions, we strongly urge that Congress consider carefully the distinctions between introductory pricing and prices of existing products.

There are few instances in which a biotechnology company has ever raised the price of a product, which in some cases was launched as long as a decade ago, and we are aware of no case in which prices were raised by more than the consumer price index (CPI). Although antitrust concerns prevent the industry from discussing pricing issues, it appears that biotechnology companies are willing and able to make a commitment to maintain price increases to CPI and would accept an appropriate enforcement mechanism to ensure this result.

However, in order to attract the substantial investments necessary to develop breakthrough drugs, biotech companies need to have flexibility in determining introductory prices. Biotechnology products are typically considered therapeutic breakthroughs; they either treat conditions for which no effective therapy existed or provide significant therapeutic advantages over existing products.

TESTIMONY

Chairman Pryor, Senator Cohen, and members of the Senate Special Committee on Aging, I am very pleased to be here today to discuss the issue of federal support for pharmaceutical research. As you know, I am here today representing the Industrial Biotechnology Association (IBA), on whose Board of Directors I serve, and the Association of Biotechnology Companies.

I am also the Chairman, President, and CEO of ICOS Corporation, a biotechnology company with 130 employees headquartered in Bothell, Washington. ICOS was formed three years ago to develop drugs based on molecules that control cell-to-cell interactions, especially in inflammatory diseases. Lest that give you the impression that I am a newcomer to this industry, I would like to add that I was recruited in 1980 to become the first President and CEO of a new biotechnology company called Amgen, which has since joined the ranks of the Fortune 500.

The biotechnology industry appreciates the Committee's concerns about drug pricing, about appropriate return on the federal research investment in pharmaceutical products, and about ensuring that patients who need these drugs have access to them. We do not believe that we as an industry can responsibly ignore these concerns. In fact, we hope to have the opportunity to work with you and with other members of this body and with the Administration to address these matters.

Those of us in biotechnology have a keen understanding and appreciation of the work conducted by the National Institutes of Health (NIH). NIH biomedical research programs contribute to our industry in important ways, direct and indirect, but we are very concerned about the "reasonable price" clause contained in NIH cooperative research and licensing agreements. **We believe that efforts on the part of any federal agency to regulate drug prices are powerful disincentives to the investment in innovation on which biotechnology companies have built a world-class industry.**

Drug Price Regulation Generally

Solutions which emphasize price regulation will adversely impact our industry's ability to attract the equity capital upon which the large majority of biotech companies rely for their research and development funding. R&D is biotechnology's biggest expense, accounting for 38% of all costs incurred by our companies. Industry-wide, that amounted to $4.9 billion in 1992, a 41% increase from 1991. A recent BusinessWeek survey comparing the R&D intensity of all U.S. industries suggests that biotechnology is our nation's most R&D intensive industry. The top five U.S. companies in R&D spending as a percentage of sales are all biotechnology companies, as are six of the top ten R&D spenders in dollars per employee.

This commitment to R&D, unmatched by any other industry in the world, is a prerequisite to making meaningful therapeutic progress against the intractable diseases which threaten the public health. Such ambitious goals require ambitious amounts of R&D funding, and the source of R&D funds for the vast majority of biotechnology companies is investors who are willing to risk their checkbooks on the future medical and commercial value of a company's research.

Unlike traditional pharmaceutical companies, biotech R&D funds do not come from existing product lines. Because most biotech companies do not currently have products on the market, at least 90% of the $4.9 billion spent on research came directly from investors, including middle class investors participating through mutual funds and pension funds. And, because biopharmaceuticals typically take 10 to 12 years to reach the marketplace, most biotechnology companies must seek investors over and over again to secure the funding necessary to conduct R&D and build manufacturing facilities.

Investors take large risks with our companies. Substantial scientific, manufacturing, and regulatory hurdles must be overcome before a new product can be marketed. Experimental therapies fall by the wayside, sometimes accompanied by their corporate sponsors. The cost of failure is compounded by the extremely high level of investment required, as well as the time between drug discovery and marketing. Very few firms have achieved profitability, while a substantial number have either folded, merged, or been taken over. In light of this already risky investment environment, the continuing capital needs of biotechnology companies can only be met if investors can foresee a return commensurate with the risks, costs, and time involved in new biotechnology product development.

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As I mentioned, I do not believe that our industry can responsibly ignore the concerns raised by this Committee and others about pharmaceutical pricing. But I would ask that, in crafting your suggested solutions, you consider carefully the **distinctions between introductory pricing and prices of existing products.**

There are few instances in which a biotechnology company has ever raised the price of a product, which in some cases was launched as long as a decade ago. I am aware of no case in which prices were raised by more than the consumer price index (CPI). Although antitrust concerns prevent the industry from discussing pricing issues, I believe that **biotechnology companies are willing and able to make a commitment to maintain price increases to CPI and would accept an appropriate enforcement mechanism to ensure this result.**

However, in order to attract the substantial investments necessary to develop breakthrough drugs, biotech companies need to have flexibility in determining introductory prices. Our products are typically considered therapeutic breakthroughs; they either treat conditions for which no effective therapy existed or provide significant therapeutic advantages over existing products.

We often compare U.S. drug prices to prices in other countries. I would note for you that **the prices of the innovative products developed by the biotech industry are generally higher in Europe and Japan than they are here in the U.S.** In Japan, the federal government sets prices for all health care providers including pharmaceutical manufacturers. The health ministry, in conjunction with MITI, establishes initial prices for biotech drugs which are very high, in some instances two or three times higher than comparable U.S. prices, in an effort to reward innovators and encourage development of new biotech products. The Japanese prices of recombinant EPO and G-CSF, for example, are more than double and triple the U.S. prices, respectively.

The Japanese government also reduces prices at a set rate for less innovative products, so as to progressively lower price levels through the years. Companies are thus provided with an incentive to maintain and improve their profitability by developing new drugs, since they are unable to rely on older products for sustained growth.

The biotech industry does not advocate such a system for the United States. But I think that the example illustrates that prices set by U.S. biotechnology companies are reasonable in comparison to prices set by foreign governments, that industrial policy considerations may dictate setting prices higher than their current levels, and that there are other valid considerations to be taken into account in the development of effective cost-containment mechanisms for our health care system.

The products developed by the biotechnology industry have brought relief for previously untreatable diseases, have proved cost-effective, and have improved the quality of life for millions of Americans. I am proud to have had a part of these achievements and am excited about future opportunities for even more dramatic advances. But biotech entrepreneurs will be able to risk capital and resources to push the boundaries of science and medicine only as long as their investors are rewarded for their successful innovations. I urge that efforts to reform our health care system and provide cost-containment be consistent with and not undermine these efforts.

The unique entrepreneurial environment in this country as facilitated the United States' undisputed position as the world leader in biotechnology. The biotechnology industry believes that proposals which weaken or destroy those incentives would be fatal to an industry which has tremendous potential -- not only to develop breakthrough therapies for our greatest public health concerns but also, as an industry of small businesses, to serve as an engine for economic growth.

Role of NIH in Biopharmaceutical Development

Let me turn now to the specific issue of collaborative research agreements with NIH.

NIH contributes to our industry in several important ways. The Institutes conduct basic research -- in their own laboratories and through the extramural grant program -- which provides fundamental knowledge about human biological processes. NIH basic research programs have helped us understand better how diseases develop in the body and how they are transmitted from person to person and from generation to generation. NIH basic research has revealed distinctions in genetic and cellular function and reproduction, identified genes associated with diseases such as cystic fibrosis and Huntington's disease, and examined the mechanisms by which the human body marshals its natural disease-fighting ability.

The university research projects sponsored by NIH also serve the additional important function of providing training to thousands of young scientists, whose skills are so necessary to our companies' efforts to develop breakthrough drugs to treat diseases for which no adequate medical therapy currently exists. IBA and ABC member companies are presently working on products to treat AIDS, Alzheimer's disease, cystic fibrosis, multiple sclerosis and other such tragic, terrifying and terminal diseases.

NIH researchers, both intramural and extramural, publish their basic research findings in peer-reviewed scientific journals that are available to scientists worldwide. The vast majority of this information does not apply, nor is it intended to be applied, directly to any specific pharmaceutical product, but instead enhances and advances the general body of available data on biological function in healthy and diseased individuals. Fundamental knowledge of this sort is the foundation on which companies build when trying to develop new therapeutic products. Biotechnology companies also carry out a substantial amount of basic research on their own -- probably more than any other industry in the world -- in an effort to better understand the processes of disease so that more targeted research and development programs can be designed.

NIH also participates in research projects with specific companies on specific products through Cooperative Research and Development Agreements (CRADAs). Although many of the CRADAs in our industry have been concluded with larger companies, smaller companies have stepped in several times to work with NIH to jointly develop drugs for which the small potential patient populations made them unattractive to larger companies.

IBA and ABC recognize the vital role that NIH research plays, both in advancing the general state of biomedical knowledge and in specific research activities performed in cooperation with individual companies. However, biotechnology companies are deeply concerned about the "reasonable price" clause contained in NIH CRADAs. With all due respect to NIH, the biotechnology industry does not believe that NIH possesses either the statutory authority or the necessary expertise to determine reasonable prices for drugs.

Our industry strongly opposes proposals that would encourage or require NIH to regulate the prices of drugs on which it collaborates with companies, just as we are similarly opposed to congressional proposals to regulate prices of drugs developed entirely by the private sector. IBA and ABC believe that drug price controls constitute a major disincentive to the willingness of companies, especially smaller companies, to license technology from, or enter into cooperative research agreements with, NIH. This would dramatically reduce the health and economic benefits of federally funded research and would, in our opinion, be inconsistent with the goals of the Federal Technology Transfer Act.

In fact, the existence of the reasonable price clause in NIH agreements, in light of its potential for mischief, already operates as a disincentive for the commercial development of NIH-funded discoveries. Several companies have informed the biotech trade associations that, for this and other reasons, they either do not license inventions from NIH or do so only under compelling circumstances.

To those who believe that NIH is "giving away" the rights to publicly funded research, we note that government reports on technology transfer show that for every $1 of federally funded research transferred to the private sector for further development, $6 of additional research is done and over $1 of tax revenue is collected. In other words, technology transfer leads to economic growth while modestly increasing tax revenues.

IBA and ABC suggest that instead of attempting to regulate the prices of products in which it plays a research role, NIH should license its technology in exchange for up-front cash

payments and/or royalties on sales, these amounts being determined by negotiation between the parties. This system is one with which our industry is familiar, having utilized it successfully for more than a decade: university technology transfer offices routinely transfer NIH-funded extramural research in this manner and biotechnology companies frequently license rights to their privately funded research to established pharmaceutical companies that are capable of manufacturing and marketing the product here in the United States or overseas. This approach would permit NIH to obtain a return that is based on the fair market value of its technology, preserve the incentive for participation in CRADAs, and generate funds with which to increase NIH's research capabilities and provide access to drugs for patients who could not otherwise afford them.

The amounts collected by NIH under these arrangements would vary, based on the stage at which the technology is transferred and the commercial value of the technology. A product that was discovered, developed and tested by NIH and is transferred to a company for manufacture and marketing will bring a larger payment and/or royalty than one which is transferred by the agency immediately after discovery and requires substantially more research and development before it can be marketed.

We note that aggregate revenues derived from licensing agreements could provide NIH with substantial additional funding, by some estimates of up to $1 billion, or perhaps more, annually. I would cite G-CSF as an example of the revenue possibilities for just one pharmaceutical product. My former company, Amgen, licensed from Sloan-Kettering important technology for the development of this product, which is used to stimulate white blood cell production in chemotherapy and bone marrow transplant patients. Amgen has paid Sloan-Kettering royalties on G-CSF alone totalling between $50 and $100 million.

Funds received from licensing could be used to support new research. These monies could also be used to provide a fund, administered by NIH or by some other agency, for use by patients who are not otherwise able to afford the product. Our industry believes that utilizing licensing proceeds in this manner would efficiently and effectively respond to the dual concerns about appropriate compensation for the federal research contribution to new drugs and about providing access to new drugs for needy patients.

We also believe that this suggestion preserves incentives for biotechnology companies to participate in NIH CRADAs. We fear that solutions which emphasize federal price setting will adversely impact on the industry's ability to attract the equity capital upon which our companies presently rely for much of their R&D funding.

We look forward to working with you to develop an equitable and effective approach to addressing your concerns about NIH support for new drug research and about health care cost containment generally.

The CHAIRMAN. Thank you very much.

Mr. Mossinghoff, are you advocating no changes in the relationship between NIH and the private pharmaceutical companies in all of this activity we have talked about?

Mr. MOSSINGHOFF. One thing that NIH might wish to do more than they are doing now is to look at the issue of royalties. That is the typical commercial situation. Dr. Rathmann mentioned one case, and there are two kinds of agreements—patent licensing agreements and CRADAs. In patent licensing agreements, the Government really has been the inventor, and with most of the CRADAs, they are not. Where the Government has really been the inventor, they enter into a patent licensing agreement. Royalties are a perfectly typical, appropriate measure of contribution. A royalty-bearing license is a usual thing for Company X and Company Y to enter into.

It is very unusual, and I would say moves toward a public utility model, when Company A licenses Company B. They don't try to get into their pricing, they just take a percentage of sales as a tribute, a royalty. That is very appropriate.

There are so many technologies out there. It is estimated there are 4,000 medical technologies looking for people to become licensees under them. The field is incredibly crowded with potential advances in medical science. Our companies themselves—we want to get you to visit some of our companies. They look more like basic research labs, and they begin to look identical to the NIH; they do an awful lot of basic research. When a project CEO decides which of these two to select, to work on, put money into, do clinical trials on, I think if you were to have a public utility model attached to the agreements with the Government, I think that would have to be a factor that the CEO would take into account in deciding the thousands of things they could put their development expertise into.

The CHAIRMAN. Mr. Mossinghoff, I am a layman in this, as you know. I would like to just state that when I first thought about the concept of royalties, I said, that is it. That is our answer right there. Let's get royalties from the companies and give that back to the Government, and plow it back into more research.

However, the more I think about royalties, the higher the prices that the drug companies charge to the American consumer, the more royalties we are going to get. I'm thinking we might be in a situation where we have a conflict of interest. We may be saying, "You go ahead and charge those higher prices, because that brings more money back to NIH, or back to the Federal Government." So, I don't know that royalties are the answer. It may be a part of the answer, but I can see a real inherent problem with royalties in this area. But a little late is better than nothing.

Mr. MOSSINGHOFF. It does follow that in the commercial established practices of patent lawyers, who know how to negotiate these royalty provisions, there are royalty standards across all the industries. It is something that is straightforward.

I think going to a pricing board with a utility model, where you need pricing data, and all the rest, it becomes a public utility-type approach. I think if you are a CEO of a company, selecting that model against the thousands of other opportunities that you have

to move toward development would discourage using this enormous capability that the NIH has, and brings to the United States' citizens.

The CHAIRMAN. You stated earlier—I think this a statement that is attributable to you, Mr. Mossinghoff—that the Government has neither the capability or the expertise to undertake the massive clinical programs and other development activities necessary for drug approval. I don't know whether that is taken out of context or what. Does this apply in research for AIDS and cancer?

Mr. MOSSINGHOFF. I don't believe, and I think probably Dr. Rathmann might want to comment here, because he really is an expert—that NIH has the capability to do the things in terms of stability, testing, manufacturing, supplies. There is an enormous amount of expertise that goes into bringing a drug from the idea or discovery through the several phases of clinical trials, to approval by the FDA, then into the marketplace. I believe that it is a true statement that NIH does not have that capability.

The CHAIRMAN. Well, it looks like we're relying on NIH quite a bit, in the pharmaceutical area, for clinical research. Am I wrong?

Mr. MOSSINGHOFF. I think there really are two things. Sometimes the CRADAs involve just basic knowledge. It is a basic knowledge-driven kind of work where the premier world scientists, fortunately, are in NIH. We in the industry want to take advantage of this tremendous expertise, so many of the CRADAs are not product-specific at all. They are really basic knowledge-specific, basic research-specific. Where there are products, sometimes the CRADA will bring them through Phase I, which is toxicology, maybe into Phase II, but I don't believe they go through Phase III, and they certainly don't go into the pharmaceutics and all of the other things necessary to bring it from an idea in a laboratory to marketplace product.

The CHAIRMAN. Should NIH be concerned about the prices that will be charged to the American consumer?

Mr. MOSSINGHOFF. I believe that system that we have in the United States is bringing price competition to the American consumer. I think the system is taking care of itself. The producer price index, I think obviously has some credit to you, Mr. Chairman, and this Committee. You certainly should take some credit for the fact that the producer price index January 1992 to January 1993 was the lowest in 15 years. It was at 5.1 percent, 46 percent below the same period the year earlier, in 1991.

There will be, as I understand, competition for many of the compounds that are developed here. That is the way the system operates and it operates very well, very efficiently.

The CHAIRMAN. I can't let that statement just stand without some response to it. I think some of these people who are trying to pay $350,000 per year for a drug, or $21,000 a year, or $10,000 a year, I don't think they are going to say that the system is working very well. I know that you have people that you have to speak for. I understand that. I have people I have to speak for. Senator Cohen has people he has to speak for. We are doing our best to see if we can't speak for them today, and try to make the system a little better.

Senator Cohen.

Senator COHEN. I was just going to follow up on Mr. Mossinghoff's praise of your work, Mr. Chairman. Are you suggesting that the threat of congressional action is what is responsible bringing prices down?

Mr. MOSSINGHOFF. I think the CEOs of our companies look at all factors when they make their decisions. The work of this Committee and the work of Senator Pryor obviously is in their minds when they decide what it is they are going to do with, in effect, carrying out their fiduciary responsibilities to their shareholders.

Senator COHEN. So in other words, if Senator Pryor or this Committee didn't take any action in the beginning of 1988 and 1989, there would have been no moderation of the prices in the marketplace?

Mr. MOSSINGHOFF. I really am not in a position to say that. There was inflation in the late 1980's, as I was quoted accurately in the press. This is really a different industry circa 1993.

Senator COHEN. Yes, but the pricing was four times higher than the rate of inflation throughout the 1980's.

Mr. MOSSINGHOFF. Really, it started down toward the later part of the 1980's. There was a major development, economically, in the industry. That was the Waxman-Hatch bill which came into effect in 1984 in which generics were speeded onto the market. That had not happened before. From 1965 to 1984, the inflation was well below the CPI. The CPI curves were up here, and we were way below that. In 1984, that was a major economic impact on the industry as a result of Waxman-Hatch. In fact, today 40 percent of the prescriptions written in the United States are generic prescriptions. That was a major effect. Whether or not these prices would have moderated, I really am not in a position to say. As you know, we cannot discuss pricing policies at PMA, and do not.

Mr. RATHMANN. I'd like to chip in a bit on the biotech side. I don't think the biotech industry's pricing, which is very favorable compared around the world—there have been very few price increases on the major products in biotech—has had anything to do with the threat of Government regulation. I think it has been responsible pricing. It has been based on products that are good. They work; they work very well; they have been priced fairly. I think comparison with international prices would reveal that. I think it is important to make that distinction.

Senator COHEN. All right, well, Senator Pryor is only effective, then, with respect to non-biomedical products. Okay, I'll draw that distinction. I'll agree. He is not effective there, and only effective in other areas.

Let me just come back to this whole issue. I am trying to make a point that Mr. Mossinghoff has made. Congress has had an important role in terms of trying to moderate or hold down the tremendous escalation of the costs of drug prices to our constituents. That is what you said?

Mr. MOSSINGHOFF. That is exactly right.

Senator COHEN. You think that is going to be sufficient as long as Senator Pryor keeps talking, or jawboning, that is going to be sufficient to do the job?

Mr. MOSSINGHOFF. Several of our major companies announced that they are limiting their price increases to the CPI. They have

all certified that they are indeed doing that. We have some issues with the Chairman about whether it is across-the-board or product-specific. I don't think there is any question they did not break their word, Mr. Chairman. I guarantee that. The companies said what they were going to do, and they are doing that. That represents almost 50 percent of the market at this point. I think other companies are in a position where they are willing to do that.

Senator COHEN. I think you indicated on one of the public programs in which you appeared with the Chairman, that you thought the staff report that was submitted to the Committee was a deception, or was deceptive. Is that correct?

Mr. MOSSINGHOFF. Well, to the extent that it said that these great American companies broke their word, that just is simply not the case, Senator. They did not break their word. What the companies said they were going to do is, across their product line, a weighted average—some drugs sell millions, some sell thousands—on a weighted average across the line, the leading companies in the industry said they were going to hold their price increases to the Consumer Price Index. Indeed, their public accountants have certified that they have done that. To the extent that it said they broke their word, that is a very serious charge that they took very seriously. I think that report was misleading.

Senator COHEN. What about the statement that the Committee report indicated that more is spent on marketing than on research? You took issue with that.

Mr. MOSSINGHOFF. No, I did not. PMA has not done any surveys of market expenditures. We do have in 1987 or 1988—Chairman Waxman, on the House side, did a survey of the 25 leading companies in the industry. There he found that marketing and research were about the same. One year one would be slightly higher, one year the other.

What I did point out, though, this is not Super Bowl advertising. This is medical symposiums, which comes under the heading of marketing; it's detailed sales representatives who call on doctors, and do a very thorough and effective job, I would submit, in letting doctors know about these new chemicals that we are producing.

Senator COHEN. You have no information how much is spent on research and development, and no information on how much is spent on marketing, or necessarily the details of what is included in that?

Mr. MOSSINGHOFF. I do have. There is a report that is produced every year. It is called the Schoenfeld and Associates Reports, which is usually published in Advertising Age and elsewhere. Their indication is that the pharmaceutical industry, and I am sure they include the over-the-counter part of the industry, spends about 5.8 percent in advertising. Marketing goes beyond advertising, but they say 5.8 percent, which is about one-third of the 16.7 percent that we spent in research and development. But that does not include the medical symposia. It does not include the sales representatives or other methods, very appropriate and effective methods, of marketing.

Senator COHEN. Did you have a chance to look at the methodology that was employed by this pharmaceutical economist out of the University of Minnesota, I believe, in terms of how he arrived at

the breakdown of how much is spent on marketing versus R&D versus profit?

Mr. MOSSINGHOFF. We are trying to get that at PMA. We would like to see that, because we don't think anybody has done any surveys that would support the kind of conclusions that we hear stated.

Senator COHEN. Of course, the difficulty is that no one is willing to furnish the information. This individual has had to draw his information from OTA, HCFA, and other types of sources.

Mr. MOSSINGHOFF. Which really don't have the data, as far as I know.

Senator COHEN. It is very tough to get, wouldn't you agree?

Mr. MOSSINGHOFF. We don't have it at PMA.

Mr. RATHMANN. We have it in the biotech industry. We'd be glad to supply it at any time.

Senator COHEN. We are going to spend more time with you, Dr. Rathmann, to find what you are doing right in this particular case.

Mr. RATHMANN. I wish you would.

Senator COHEN. Just one more question, Mr. Mossinghoff.

I take it you think that the reasonable price clause that is contained in these CRADA agreements is not something worth pursuing? It ought to be dropped?

Mr. MOSSINGHOFF. Well, we are not recommending that, certainly. But I would say what I would urge against is to put enough burden, a public utility burden, on these CRADAs so that they become very unattractive. We also will not lecture our companies in our boardrooms about whether they are or are not going to enter into future agreements with anyone. That is just not appropriate for a trade association of competitors. But there are reported cases where some leading companies have already been discouraged by the pricing clause that is in those contracts.

Senator COHEN. You indicated you can terminate a CRADA if there is a breach of the pricing agreement. I think we have already heard today that there is no way that NIH has the ability to determine whether there has been a breach of that agreement.

Mr. MOSSINGHOFF. The clause itself is, as you point out, certainly not a self-enforcing clause.

Senator COHEN. But they don't even have the ability. They are in the business of research and science. They don't have a bevy of either attorneys or accountants or GAO types overseeing these contracts.

Mr. MOSSINGHOFF. Thankfully.

Senator COHEN. You say thankfully, and I raise the issue of why have them at all? The notion is that you are going to have a clause in there that you are going into a reasonable pricing agreement, which in fact they don't have the expertise to negotiate in the first instance. Number two, they don't have the ability to monitor it. They don't have the ability to enforce it. Why have it? Do you like the spirit of it?

Mr. MOSSINGHOFF. I won't differ with you on that, if that is the proposal.

Senator COHEN. Do you think it is better than something we might propose as an alternative, though?

Mr. MOSSINGHOFF. No, I would be concerned if there were a pricing—again, we have had a lot of experience in the United States with public utilities. All the electric people, they know how to live with that. My background is in electrical engineering and construction. I don't know when the last invention came out of a public utility. That is not what public utilities do. People know how to do pricing commissions. I don't know if they do it well or not well, but they know how to do it. Adding that kind of an approach to a CRADA, I would guess—and I am just guessing—but we won't let our companies tell us what they are going to do in the future. I would think that would probably drive a lot more companies into the column that say, we've got thousands of other opportunities; this is not one we are going to put our shareholders' money into.

Senator COHEN. You may have thousands of other opportunities, but you are going to find that if the prices continue at the retail level—and I don't know about how these prices have been held down—you talk about the average, the weighted average, you charge more on some and less on others—out in the real world where they are buying these, people can't afford them. Drugs that they have been using for years have gone up not once a year, two, three, sometimes four times within a 1- or 2-year period.

Mr. MOSSINGHOFF. For drugs that have been on the market for a long time.

Senator COHEN. They are not seeing the benefit in their pocketbooks of what you claim is going on in the way of restraint.

Mr. MOSSINGHOFF. Part of the answer there has got to be access. The PMA board has taken a very forthright position. We want to work with you and Senator Pryor and the Administration to make sure that in any managed competition benefit, that one of the basic benefits includes prescription drugs.

For years we have had a position that Medicaid drugs should be provided at 100 percent of the Federal poverty level. We want to work with you on any issue having to do with Medicare patients.

Senator COHEN. Let me suggest to you that if the pharmaceutical industry wants to be included in this health care reform, which includes managed competition, you will probably find some pretty serious price controls in there.

In other words, what you would like to see is drugs included as far as coverage, but with no restraint on the pricing. That isn't going to happen.

Mr. MOSSINGHOFF. There is restraint. There is restraint happening right now. The data is absolutely clear that whenever you see price increases decrease by 46 percent in 1 year, I don't think it is fair to say there is no restraint.

Senator COHEN. You already said that Senator Pryor is responsible for that.

Mr. MOSSINGHOFF. I think he should take some credit for it, honestly and sincerely.

The CHAIRMAN. I don't want to take any credit, but I'll take whatever blame you want to pass out about a couple of things.

Our local pharmacist in Little Rock the other morning, said he had gotten three price increases already since December 1, pretty well across-the-board. Is that going to continue? You say that you

are holding down. How can he have already gotten three price increases since December?

Mr. MOSSINGHOFF. What I said, Mr. Chairman, is what the companies said. They do this independently. We really have to be very, very careful. We can't talk about price increases in the PMA boardroom. It is just off limits as far as anti-trust laws. Companies, individually, I think 10 companies now have said that they will hold their across-the-board, weighted-average price increases to be no more than the Consumer Price Index, or the projected Consumer Price Index. They have certified, and their accountants have certified that, indeed, they have kept those pledges.

The CHAIRMAN. Senator Cohen in one of his questions mentioned the gentlemen from Minnesota, Dr. Schonelmyer. I understand that he has obtained research data from HCFA and from OTA that the Aging Committee has used about prices. I don't know what methodology he actually used, but that is the source, in case the pharmaceutical people want to check in with him.

Mr. MOSSINGHOFF. Not on promotion, Senator. There is nothing I know about what HCFA or OTA has on marketing. There is the Schonfeld Advertising, that is a matter of public record, published in Advertising Age every year. That is the 5.8 percent of sales, again, as compared to 16.7 in research and development.

I don't believe there are any data to reach the conclusions that have been reached.

The CHAIRMAN. I don't know what method he used, but maybe he added up all the expenditures of the companies, and what was left he couldn't account for and said that was marketing. I'm not sure.

Mr. MOSSINGHOFF. We've asked him to see if we couldn't have our people take a look at what he did have.

The CHAIRMAN. Let me cooperate with you on that, because I do not want to be guilty of using misleading figures. I do not want to be. I want to use accurate figures. Maybe you and the PMA and the people you represent, Senator Cohen and myself, maybe we could all decide on a series of questions to pose as to how that data was actually obtained.

Senator COHEN. Could we strike an agreement that we would be willing to work to analyze his figures and his analysis, if the drug manufacturers will share their information with us so we can find out what they have?

The CHAIRMAN. They are not going to share their information.

Mr. MOSSINGHOFF. Senator, there is a development. I was privileged to testify Monday before your colleague, Chairman Waxman, on the House side. He did ask, and we are working now to see what confidentiality agreements can be given by him, which he has done before. He has asked these questions of the top 15 companies in the industry. I think given the right pledge of confidentiality, I have no question that those companies will respond.

The CHAIRMAN. About 2 years ago we made contact with the Astra Pharmaceutical Company about Foscavir, we said, "Please tell us how much money you put into R&D, and now how much you are getting out." They said, "On one condition." We said, "What?" They wanted to come and administer an oath of secrecy to me in

the office. If they told me information, I would swear not to reveal it. I didn't do it. I think that is carrying it a little bit far.

A new source of competition to Burroughs Wellcome for AZT has now been found. The government is tied up in a lawsuit over that new source. Burroughs Wellcome has the original license. Why would Burroughs Wellcome fear this competition in this field right now? They sold $1.4 billion in the last 3 to 5 years. Why would they fear this competition?

Mr. MOSSINGHOFF. Mr. Chairman, I have difficulty answering for a company. I don't think it is appropriate for me to do that. But I can say that as things stand right now, and it is in patent litigation, Burroughs Wellcome doesn't have a license; they own the patent. They are the presumed patent owners. The issue of who invents an invention is something patent lawyers litigate all the time. There is a huge body of law on that. That is coming to trial. They are not licensees of anyone. They are owners of the patent. They are the inventors, at least that's the situation until it is determined otherwise, on the record.

The CHAIRMAN. That is being disputed by NIH. We want the record to show that.

Mr. MOSSINGHOFF. It is really being disputed by Barr Laboratories in litigation. I think NIH asked to be dismissed from that suit, and has been.

The CHAIRMAN. I have no further questions. I want to thank you, Mr. Mossinghoff, and thank you, Dr. Rathmann. We look forward to continue trying to solve some of these problems and answer some of these questions.

Thank you very much. Our hearing is adjourned.

[Whereupon, at 12:25 p.m., the Committee adjourned, to reconvene at the call of the Chair.]

APPENDIX

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

THE FEDERAL GOVERNMENT'S INVESTMENT IN NEW DRUG RESEARCH AND DEVELOPMENT:

ARE WE GETTING OUR MONEY'S WORTH?

Background Information
prepared by the staff for hearing of the

United States Senate
Special Committee on Aging

Senator David Pryor, Chairman

Wednesday, February 24, 1993

This document has been printed for information purposes.
It does not represent either findings or recommendations
formally adopted by the Committee.

CHARTS, TABLES AND GRAPHS

Chart 1 - Hearing Questions

Chart 2 - Federal Government Provides Extensive Support for New Drug R&D. (This chart shows the various ways in which the federal government directly and indirectly supports the discovery, research, and development of new pharmaceuticals.)

Chart 3 - Federal Government Involved in Development of Many New Drugs. (This chart provides specific examples of drugs that have been discovered or developed with federal resources, and the nature of the federal government's involvement.)

Chart 4 - The US National Institutes of Health is the Organization with the Most Drugs in R&D...121...But Most of the Active Compounds will be Licensed Out. (This chart shows that, in 1992, the NIH was the organization with the most drugs in development in the United States.)

Chart 5 - Cost of Select AIDS and Cancer Drugs. (This chart shows the involvement of the federal government in the development of certain drugs to treat cancer and AIDS. Also included are the current prices for these drugs, and the cost to federal health care programs to buy some of these drugs.)

Chart 6 - OPTIONS. (This chart describes six options that can be considered -- either alone or in combination -- to assure that drugs which are developed with substantial federal resources or through CRADAs are priced "reasonably.")

Chart 7 - AZT Sales, 1987-1992. (This chart shows a year by year breakdown of the total worldwide sales of AZT (Retrovir), which is manufactured by Burroughs-Wellcome. The drug is used alone and in combination with other drugs to treat HIV infection.)

Chart 8 - Selected Drugs Used to Treat HIV Disease. (This charts shows the retail costs of several drugs used to treat HIV and related conditions associated with HIV, such as anemia (EPO), eye infections (Foscarent, also known as Foscavir), and other bacterial infections (Azithromycin, Clarithromycin)).

Letter 1 - Letter from Secretary Sullivan to Senator Pryor. It details the $22 million in clinical trials which were supported by the NIH to demonstrate the efficacy of Foscarnet in treating CMV retinitis, an common eye infection in AIDS patients.

Letters 2 & 3 - These two letters show that the National Cancer Institute (NCI) was the first organization to apply for and receive the orphan drug designation on DDC in 1986. Hoffman-LaRoche then later applied for and received the orphan drug designation and the 7-year market exclusivity about a year and a half later, in 1988.

HEARING QUESTIONS

1. What are the various ways in which the federal government supports new drug R&D?

2. Are appropriate mechanisms in place to assure that the federal government's investment in new drug R&D is adequately protected?

3. Should the determination of "reasonable price" for a drug developed with federal government support be a responsibility of the National Institutes of Health (NIH)?

4. If the responsibility for determining a "reasonable price" is not vested with NIH, how should it be determined?

5. What information is needed, both from the NIH and the manufacturer, to determine that a price is "reasonable"?

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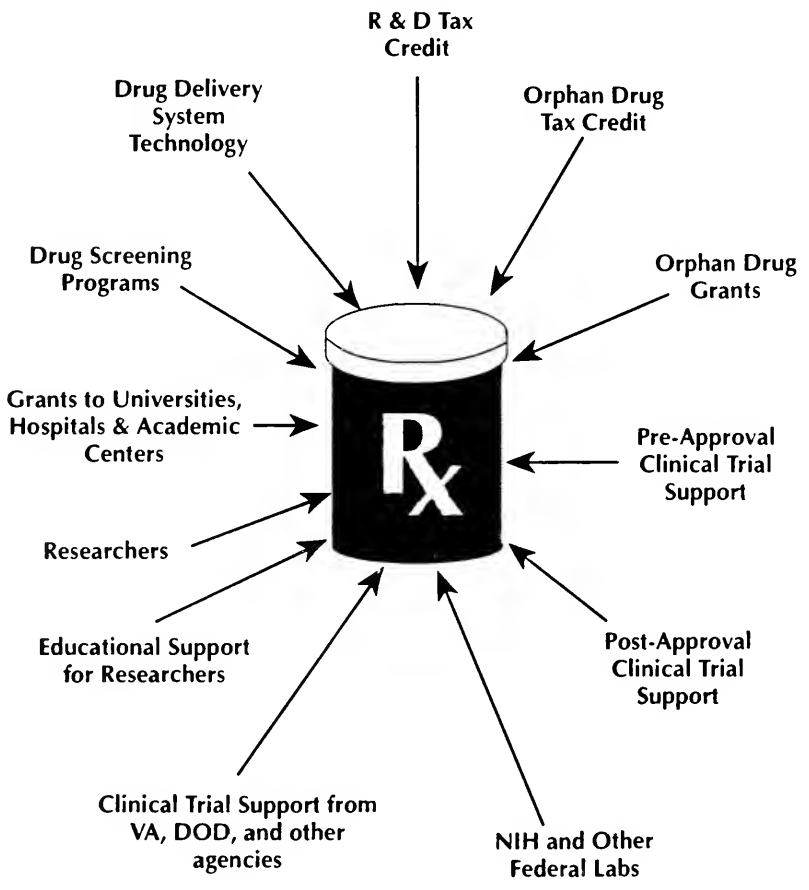
FEDERAL GOVERNMENT PROVIDES EXTENSIVE SUPPORT FOR NEW DRUG R & D



Source: Senate Special Committee on Aging

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FEDERAL GOVERNMENT INVOLVED IN DEVELOPMENT OF MANY NEW DRUGS

TYPE OF FEDERAL INVOLVEMENT	EXAMPLE
CRADA* Drugs	Taxol, Recombinant Alglucerase
Non-CRADA Drugs	AZT, DDC, Foscavir, Placental Alglucerase
Exclusive Licensing Agreement	DDI
Delivery System Technology	Nicotine Patches
Drugs Developed with Federal Grants Given to Hospitals/Universities	Interleukin-2
Biological Proteins Purified/Discovered by Federal Labs	Placental Alglucerase, EPO
Clinical Trial Support (Pre-FDA Approval)	AZT, DDC, DDI, Foscavir, Taxol, Levamisol
Orphan Drugs	Ceredase, EPO, HGH, Pentamidine

*Cooperative Research and Development Agreements

Source: Senate Special Committee on Aging

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"THE US NATIONAL INSTITUTES OF HEALTH IS THE ORGANIZATION WITH THE MOST DRUGS IN R&D. . .121. . .BUT MOST OF THE ACTIVE COMPOUNDS WILL BE LICENSED OUT. . ."

RANKING	ORGANIZATION	NUMBER OF OWN DRUGS (1)	NUMBER OF LICENSED DRUGS (2)	TOTAL
1	NIH	77	44	121
2	Smith Kline	79	40	119
3	Merck	96	19	115
4	Lilly	90	25	115
5	Ciba-Geigy	75	33	108
6	Bristol	83	24	107
7	Roche	79	26	105
8	Warner Lambert	79	25	104
9	Marion	68	28	96
10	American Home	66	27	93

SOURCE: SCRIP Review, 1992

(1) - Drugs that were discovered and are under development by the organization.
(2) - Drugs that are under development by the organization, which were licensed form other companies, universities, or academic centers.

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COST OF SELECT AIDS AND CANCER DRUGS

DRUG/ USE/ MFGR	FEDERAL INVOLVEMENT	PRICE/ COMMENTS
AZT (HIV/AIDS) BURROUGHS	• Activity against HIV reportedly discovered by NCI. • Many pre and post marketing clinical trials supported by NCI and NIAID.	• @ $2,000-3,000/yr • Medicaid primary payer of drug • Ryan White program a significant payer • Manufacturer has earned $1 billion in worldwide sales.
FOSCAVIR (HIV/CMV Retinitis) ASTRA	• $22 million in various clinical studies supported by NIH.	• @ $21,000/yr
DDC (HIV) ROCHE	• Originally discovered by NCI. • FDA designated NCI as orphan drug sponsor in 1986. • Orphan drug.	• @ $1,800-2,000/yr
EPO (Anemia of HIV) AMGEN ORTHO	• Protein Purified by Federal Labs. • Orphan drug	• @ $10,000/yr • Medicare primary payer through ESRD program • Federal costs est to be $1 billion since 1989.
LEVAMISOL (Colon Cancer) JOHNSON & JOHNSON	• $11 million spent by NCI to determine effectiveness against colon cancer.	• $6 per tablet, which is 100 times cost of same drug used for sheep - 6 cents
TAXOL (Ovarian Cancer) BRISTOL MYERS	• NCI invented and discovered drug. • Estimated $32 million spent on pre-clinical and clinical trials by NCI.	• $9,350 for full 8 cycle treatments

Source: Senate Special Committee on Aging

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OPTIONS

OPTION		DESCRIPTION
1.	CURRENT POLICY-REVIEW PRICE	Continue Current Policy -- NIH reviews, but does not audit, the price determined by the manufacturer as "reasonable".
2.	ROYALTY	Require Manufacturer to Pay "Royalty" to Federal Government on federally-developed drug. Royalty based on contribution made by federal government. Royalties can be used for additional research activities or can be deposited into a "dedicated" fund.
3.	PRICE BID	"Reasonable price" for a drug discovered and/or developed by federal labs determined by independent board, which is then put out for bid among manufacturers. Manufacturers then have to compete to obtain a license for the drug from the federal government. Board awards bid based on combination of factors, including price.
4.	PRICE NEGOTIATED	Independent Board negotiates "reasonable price" with manufacturer based on data provided to it by NIH and by manufacturer. Factors such as potential market for drug, federal R&D costs, manufacturer production and R&D costs, considered when determining price.
5.	REDUCE EXCLUSIVITY	Reduce the market exclusivity or licensing period for any federally-developed drug whose price increases over inflation, or when sales of the drug reach a certain level.
6.	MEDIAN PRICE	Allow the manufacturer to charge no more than the median price for drugs in the same therapeutic class.

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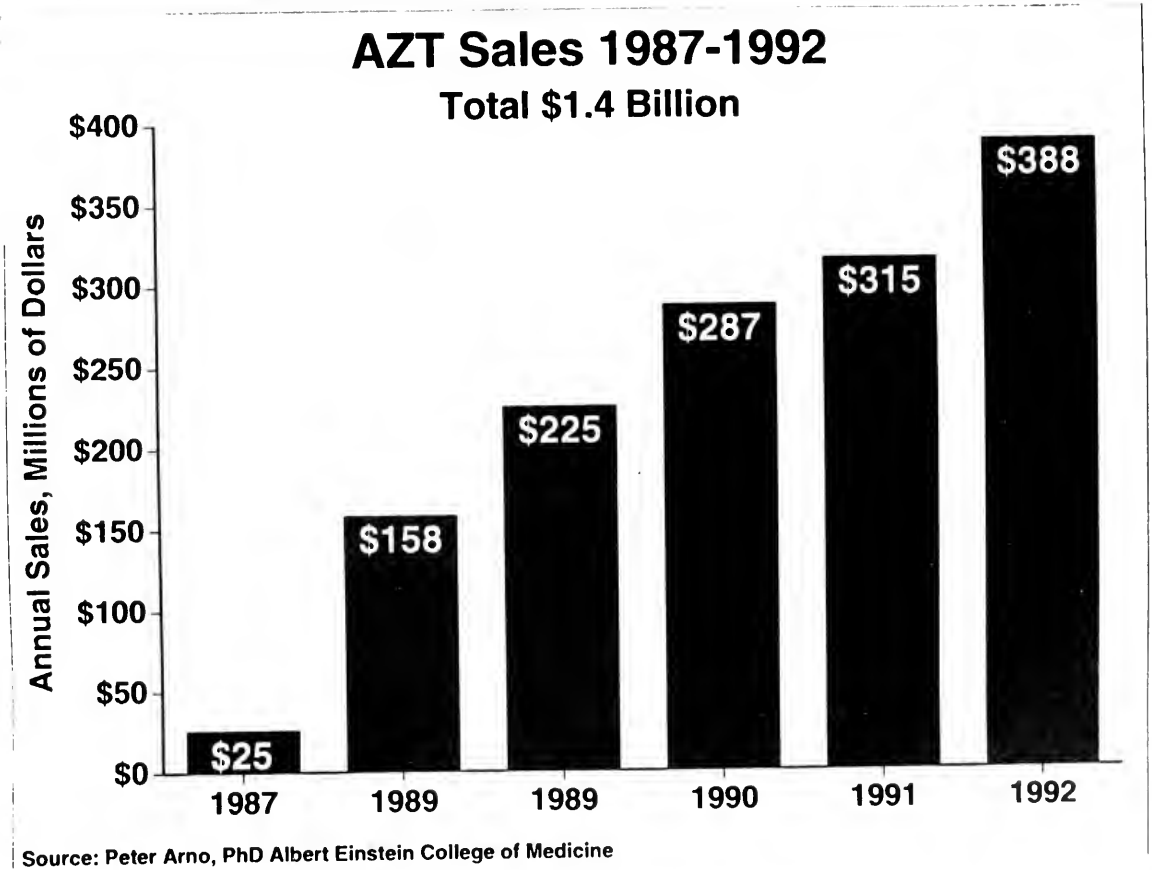
AZT Sales 1987-1992
Total $1.4 Billion
Annual Sales, Millions of Dollars
$400
$350
$300
$250
$200
$150
$100
$50
$0
$25
$158
$225
$287
$315
$388
1987
1989
1989
1990
1991
1992
Source: Peter Arno, PhD Albert Einstein College of Medicine

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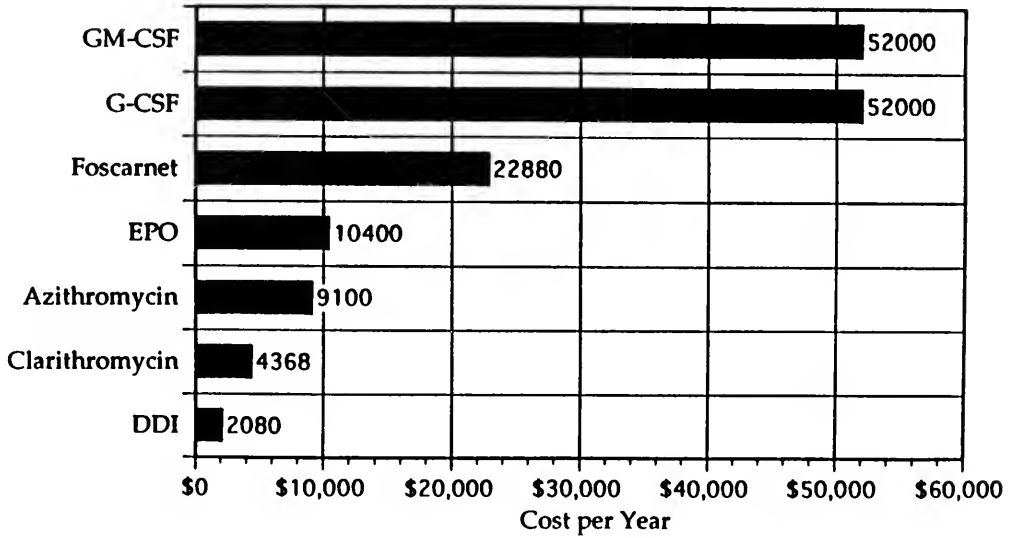
Selected Drugs Used to Treat HIV Disease
Retail Cost per Year



Source: Fred Hellinger, Ph.D., *Inquiry* 1992;29:363

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

APR 10 1992

The Honorable David Pryor
Chairman, Special Committee on Aging
United State Senate
Washington, D.C. 20510

Dear David:

This is in response to your inquiry concerning the pricing of foscarnet, a drug recently approved by the Food and Drug Administration (FDA) for the treatment of cytomegalovirus (CMV) retinitis in HIV-infected individuals, and your request for a comprehensive assessment of the role of the National Institutes of Health (NIH) in the research and development of this drug. The NIH was not involved in the preclinical development of foscarnet. The NIH's primary involvement with this agent has been through its clinical trials programs, which evaluated the safety and efficacy of foscarnet.

The National Eye Institute (NEI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Cancer Institute (NCI) have sponsored an intramural and several extramural clinical studies evaluating foscarnet for the treatment of CMV retinitis in HIV-infected individuals, as well as other HIV-related applications. Specific information on these studies and estimates of their cost are provided in the enclosed project list.

In reviewing this information, it is important to make two distinctions. First, the majority of studies supported by NIH on foscarnet were not related to the new drug application (NDA) submitted to the FDA by Astra Pharmaceuticals, Inc., for the approval of foscarnet (trade name Foscavir) in 1991. The information provided thus differentiates between NIH-sponsored foscarnet studies that were included as part of the NDA and other studies of foscarnet that were not related to the Astra NDA.

Second, it should be pointed out that the NIAID does not, at this time, have a means to specifically determine the costs of its clinical trials by protocol. The NIAID has established the AIDS Clinical Trials Group (ACTG), which consists of a nationwide network of clinical sites to evaluate potential therapies for HIV infection and HIV-associated opportunistic infections (OIs) and malignancies. The ACTG program provides scientific and medical expertise, operational support for the development and conduct of clinical trials, and statistical and data management capabilities. It is not currently possible to determine the

exact costs associated with any one protocol or drug since the ACTG is supported as a whole by an operations center and a statistical and data management center, and because individual ACTG institutions incur varying costs for the protocols in which they participate. Thus, the NIAID funding levels provided in the enclosure represent the NIAID's best estimate of the costs associated with their foscarnet protocols.

The NIH was not involved in the discovery or preclinical development of foscarnet and, consequently, has no patent rights to this drug. All patents have been filed by Astra and are the property of the company.

In your letter, you suggested that HCFA might be able to undertake a study of Foscavir, similar to the study it conducted of recombinant erythropoietin (rEPO). The unique circumstances of rEPO, including that it was the first drug developed by a new company and there was a willingness of the manufacturer to participate in the analysis of its development costs, are not transferrable to the Foscavir situation. HCFA is not in a position to conduct a similar analysis for Foscavir.

We would suggest that a detailed analysis of the total cost in bringing Foscavir to market would require information available solely from Astra Pharmaceuticals, Inc. We appreciate your interest and support of the Department of Health and Human Services's AIDS-related activities.

Sincerely,

Louis W. Sullivan, M.D.

Enclosure

National Institutes of Health (NIH)

Studies Related to Foscarnet

The NIH-sponsored studies on foscarnet for cytomegalovirus (CMV) retinitis that were included as part of Astra Pharmaceuticals new drug application (NDA) for the approval of foscarnet are as follows:

Intramural: The National Eye Institute (NEI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI) and the NIH Warren Grant Magnuson Clinical Center supported an intramural clinical trial entitled "A Randomized, Controlled Trial of Foscarnet in the Treatment of Cytomegalovirus Retinitis in Patients with AIDS." The study, which accrued 24 patients, was opened for enrollment in November 1988 and was closed in January 1990. The results of this trial demonstrated that the administration of foscarnet decreases the rate of progression of CMV retinitis in persons with AIDS. This study was published in the November 1991 issue of the *Annals of Internal Medicine*.

The total costs incurred by NIH for this study are estimated to be $1.7 million. Astra provided additional support for this study.

Extramural: The NIAID AIDS Clinical Trials Group (ACTG) sponsored a protocol (ACTG 015) entitled "Foscarnet Treatment of Serious CMV Retinitis Infection in Patients with AIDS," which was opened for accrual in November 1987. This phase I/II trial accrued a total of 59 patients prior to closing in May 1989. The purpose of the study was to evaluate the safety and efficacy of three doses of intermittent intravenous foscarnet in the treatment of acute CMV retinitis infections in AIDS patients.

The total costs incurred by NIAID for this study are estimated to be $1.35 million.

The NIH-sponsored studies of foscarnet in patients with HIV/AIDS that were not included in the Astra NDA, but represent part of the NIH's activities in the evaluation of foscarnet, are as follows:

- **ACTG 129:** The NIAID and the NEI co-sponsored, through the ACTG and the Studies of the Ocular Complications of AIDS (SOCA) programs respectively, a protocol entitled "Foscarnet-Ganciclovir CMV Retinitis Trial." This was a phase III clinical trial that opened in March 1990 and accrued approximately 240 patients. The trial was closed in October 1991 because the data indicated that patients treated with foscarnet lived on average four months longer than those patients treated with ganciclovir. Foscarnet and ganciclovir, however, appeared to be equally effective in halting the progression of CMV retinitis and preserving vision. The total NEI costs for the study, conducted as part of the SOCA program, was $9.0 million. The total NIAID costs for the study are estimated to be $4.4 million.

  Astra provided foscarnet at no cost for the patients enrolled in this study (as well as the NIH intramural study and ACTG 015 listed above). Although ACTG 129 was stopped on October 7, 1991, Astra will continue to provide each patient with the drug, at no cost, for the duration of the follow-up study that will last at least until September 1992. In addition, Astra provided $600,000 to the SOCA Coordinating Center at the Johns Hopkins University School of Public Health and Hygiene for statistical analyses related to the usefulness of foscarnet in this study population as well as the drug toxicity monitoring for this study, as required by the Food and Drug Administration (FDA).

  To the best of our knowledge, foscarnet was approved before the ACTG 129 protocol results were made available to the FDA. Therefore, it is questionable whether any portion of the cost of ACTG 129 should be attributed to the development of this drug.

- **ACTG 028:** This small phase I study was initiated in May 1988 under a NIAID Investigational New Drug application (IND), and accrued 9 patients. The purpose of this study was to determine the toxicity of low dose foscarnet in HIV-positive symptomatic and asymptomatic patients with CD4 counts less than 500 cells/mm³. This study closed in November 1989.

The total costs incurred by NIAID for this study are estimated to be $206,000.

- **ACTG 053:** This small phase I study was initiated in November 1988 under a NIAID IND, and accrued 6 patients. The purpose of this study was to examine the toxicity, pharmacokinetics, and antiretroviral efficacy of combined oral AZT and intermittent intravenous foscarnet therapy in AIDS or AIDS-Related Complex (ARC) patients who received AZT for 8-52 weeks. This study closed in September 1989 and the results are published.

  The total costs incurred by NIAID for this study are estimated to be $138,000.

- **ACTG 093:** This phase II trial was initiated in March 1989 under a NIAID IND, and accrued 170 patients. The purpose of this study was to evaluate the tolerance and efficacy of foscarnet in patients who could not tolerate ganciclovir or whose infection was resistant to ganciclovir. This study closed in June 1990.

  The total costs incurred by NIAID for this study are estimated to be $3.9 million.

- **ACTG 095:** This phase III trial was initiated in June 1989 under a NIAID IND, and accrued 26 patients. The purpose of this study was to compare the efficacy and toxicity of foscarnet and vidarabine when used to treat mucocutaneous herpes simplex virus infection that had demonstrated resistance to acyclovir in HIV-infected individuals. The study closed in October 1990 and the results are published.

  The total costs incurred by NIAID for this study are estimated to be $596,000.

- **ACTG 136:** This pharmacology study accrued 7 patients in August 1990 and has been completed. The purpose of this study was to determine the effect of increasing gastric pH on the extent of absorption of oral foscarnet in asymptomatic HIV-infected patients and patients with early ARC.

  The total costs incurred by NIAID for this study are estimated to be $160,000.

- **ACTG 151:** This phase I trial was opened to accrual in May 1991 and has accrued to date 18 patients. The study targets accrual of 30 patients. The purpose of this study is to examine the safety and tolerance of concurrent and alternating regimens of ganciclovir and foscarnet and the interactive pharmacokinetic profile of long-term combined and alternating treatment with ganciclovir and foscarnet.

  The costs incurred by NIAID to date for this study are estimated to be $413,000.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 9 1986

National Cancer Institute, The Division of Cancer Treatment
Attention: Eddie Reed, M.D.
Special Assistant for Pre-clinical Science
Building 31, Room 3A49
National Institutes of Health (NIH)
Bethesda, Maryland 20892

Dear Sir:

Reference is made to the application of October 17, 1986 submitted on behalf of the National Cancer Institute (NCI) of the National Institutes of Health (NIH) pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 360bb) for the designation of 2'-3'-dideoxycytidine as an orphan drug.

We have completed our review of the information submitted in accordance with the Food and Drug Administration Interim Guidelines implementing section 526 of the FFDCA and have determined that 2'-3'-dideoxycytidine qualifies for orphan designation for use in the treatment of acquired immune deficiency syndrome (AIDS). This letter is official notification of designation.

The enactment of Public Law 99-91 amended section 527 of the FFDCA (21 U.S.C. 360cc) to remove the condition that non-patentability of a designated drug be demonstrated prior to eligibility of that drug for orphan drug exclusivity. Prior to marketing approval, sponsors of drugs that have been designated as orphan drugs are requested to submit written notification to the Office of Orphan Products Development of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted for the statutory period of exclusivity.

Sincerely yours,

Stephen Fredd M.D.

Stephen B. Fredd, M.D.
Acting Director, Office of Orphan
Products Development

DEPARTMENT OF HEALTH AND HUMAN SERVICES

June 28, 1988

Mary Ellen Mulligan
Assistant Director
Drug Regulatory Affairs
Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, New Jersey 07110

Dear Ms. Mulligan:

Reference is made to the application of March 7, 1988 and amendment thereto of June 9, 1988 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 360bb) for the designation of 2'-3'-dideoxycytidine as an orphan drug.

We have completed our review of the information submitted in accordance with the Food and Drug Administration Interim Guidelines implementing section 526 of the FFDCA and have determined that 2'-3'-dideoxycytidine qualifies for the orphan designation for use in the treatment of acquired immune deficiency syndrome (AIDS). This letter is official notification of designation.

Prior to marketing approval, sponsors of drugs that have been designated as orphan drugs are requested to submit written notification to the Office of Orphan Products Development of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another sponsor for the statutory period of exclusivity. In addition, please inform this office semiannually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of 2'-3'-dideoxycytidine as designated.

Sincerely yours,

Marlene E. Haffner, M.D.
Director, Office of Orphan
Products Development (HF-35)

NAME *Generic/Chemical* *TN=Trade Name*	INDICATION DESIGNATED	SPONSOR & ADDRESS *DD=Date Designated* *MA=Marketing Approval*
URSODEOXYCHOLIC ACID TN= URSOFALK	TREATMENT OF PATIENTS WITH PRIMARY BILIARY CIRRHOSIS.	INTERFALK U.S., Inc. 25 MARGARET STREET PLATTSBURGH NY 12901 DD 06/20/91 MA / /
VILOXAZINE HCL TN= VIVALAN	TREATMENT OF CATAPLEXY.	STUART PHARMACEUTICALS DIVISION OF ICI AMERICAS WILMINGTON DE 19897 DD 06/11/84 MA / /
VILOXAZINE HCL TN= VIVALAN	TREATMENT OF NARCOLEPSY.	STUART PHARMACEUTICALS DIVISION OF ICI AMERICAS WILMINGTON DE 19897 DD 06/11/84 MA / /
ZALCITABINE TN= DDC	TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).	NATIONAL CANCER INSTITUTE, DCT BLDG 31, ROOM 3A49, MIH BETHESDA MD 20892 DD 12/09/84 MA / /
ZALCITABINE TN= HIVID DDC	TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).	HOFFMANN-LA ROCHE, INC. 340 KINGSLAND STREET NUTLEY NJ 07110-1199 DD 06/28/84 MA / /
ZIDOVUDINE TN= RETROVIR AZT	TREATMENT OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS).	BURROUGHS WELLCOME COMPANY 3030 CORNWALLIS ROAD RESEARCH TRIANGLE PK NC 27709 DD 07/17/85 MA 03/19/87
ZIDOVUDINE TN= RETROVIR AZT	TREATMENT OF AIDS RELATED COMPLEX (ARC).	BURROUGHS WELLCOME COMPANY 3030 CORNWALLIS ROAD RESEARCH TRIANGLE PK NC 27709 DD 05/12/87 MA 03/19/87
ZINC ACETATE TN=	TREATMENT OF WILSON'S DISEASE.	LEMMON COMPANY 650 CATHILL ROAD SELLERSVILLE PA 18960 DD 11/06/85 MA / /

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

March 13, 1993

Bruce Chabner, M.D.
Director, National Cancer Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, MD. 20205

Dear Dr. Chabner:

We are writing to follow up on a request that we made of you during your recent appearance at the February 24th, 1993 Senate Aging Committee hearing on the Federal government's involvement in new drug research and development. During a question and answer period, you indicated that you could provide the Committee with data and information relating to the NIH's contribution to the discovery, research, and development of AZT (zidovudine).

We would like to officially request that you provide as detailed a description as possible of the financial investment made by the federal government in the discovery and development of AZT, as well as DDC and DDI. We would appreciate a description of each activity or NIH-subsidized clinical trial that was conducted on these drugs both before and after FDA approval. Please include both intramural and extramural activities that were supported by the NIH, and the estimated cost of each activity or trial to the federal government. Please include an estimated total federal government dollar investment for the development of each drug.

We appreciate your taking the time to testify at the hearing, and providing insight into the role of the NCI in discovering and developing cancer and AIDS drugs. Any questions about this particular request can be directed to John Coster at the Senate Special Committee on Aging, 202-224-5634. We thank you for your attention to this request, and would certainly appreciate as prompt a reply as possible.

Sincerely,

William S. Cohen
Ranking Minority Member

David Pryor
Chairman

genzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562
617-252-7500
TLX 201223 GENCAMB
FAX 617-252-7500

February 22, 1993

The Honorable David Pryor, Chairman
Special Committee on Aging
SR-267 Russell Senate Office Building
Washington, DC 20510-0402

Dear Senator Pryor:

In the February 22, 1993 issue of *BioCentury*, The Beinstein Report on Business, an article written by Kris Herbst reports that Dr. Judith Wagner, senior associate of the congressional Office of Technological Assessment, will discuss Ceredase before the Senate Committee on Aging on Wednesday, February 24, 1993. This article refers to the OTA background paper on Ceredase prepared last October and the article makes three comments, two of which refer to the report and a third which is attributed to an OTA senior analyst. These comments need a significant clarification if they are to be used by you and your committee.

The article says the OTA concluded "it was impossible to estimate the extent to which depreciation expenses included in the unit cost estimates either understate or overstate the true costs of manufacturing and marketing Ceredase." This is taken out of context of the report since the report says "depreciation charges probably do not reflect the true economic cost of such facilities, however, because they are only a very rough and imperfect approximation of the actual loss of market value of the assets in each year." In fact our accounting for depreciation follow generally accepted accounting principles which amortize the cost of the asset over its useful life. Those depreciation costs as calculated are reflected in the unit costs of production. Consequently, it is not "impossible" to estimate.

In fact if one were to depreciate the true economic cost of such facilities the depreciation in all likelihood would be higher since the assets in fact were purchased at a lower historical cost than the higher replacement costs.

The article and report then state that the OTA does "not report the internal rate of return to the private investments in Ceredase because it is impossible to determine the true contribution of Ceredase revenues to repaying the R&D investment".

We provided the OTA with an internal rate of return calculation encompassing the life cycle of Ceredase from the completion of clinical trials through ten years of commercialization a total of 12 years. That calculation included all expected revenues and costs including those from overseas sales of Ceredase and the actual and anticipated investments that are necessary to build and pursue any business including not only the R&D effort but also the investment required to put the production capacity in place to manufacture Ceredase and the working capital needed to support the business.

The final point in the news article quotes Dr. Michael Gluck, an OTA senior analyst as describing "the difficulties in trying to get anything useful from Genzyme, even though they provided data that they considered confidential". Since the outset of the OTA study Genzyme has been totally cooperative, has provided all the data requested and in fact volunteered more data than requested in order to provide a complete analysis. The inference is that we were uncooperative. That is far from the case.

We have taken exception with many conclusions drawn by the OTA report and I would suggest that any information derived by you from that report or from the authors be evaluated extremely carefully.

There is no question that the issue of developing and bringing dramatic treatments to people in need is a complex and perhaps sensitive one. There are aspects of this issue which can be open to interpretation by any individual with a specific agenda. It is imperative that you start the discussion by getting and using factually correct information.

Sincerely,

David J. McLachlan
Senior Vice President - Finance

cc: J. M. Coster, Ph.D.
Judith L. Wagner, Ph.D.

genzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
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617-252-7500
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Statement by Genzyme Corporation to the Special Committee on Aging

Genzyme Corporation agrees with the Office of Technology Assessment (OTA) that the Federal government's involvement in the development of Ceredase® is a shining example of the benefits of government-industry cooperation.

The data used in the OTA report, Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease was compiled approximately one-year after market introduction of Ceredase®. Therefore, certain information contained in the testimony given today by Judith L. Wagner, Ph.D., Senior Associate, of the Office of Technology Assessment are outdated, misleading and inaccurate.

1. Gross margins for Ceredase are Below Industry Standards

Genzyme estimates the 1992 cost to produce Ceredase® is $2.74 per unit versus net selling price of $3.50 per unit. This represents a contribution well below normal pharmaceutical margins.

According to the OTA report on Ceredase®, total costs to produce the product is $1.90 per unit. The annual cost of Ceredase® therapy at $1.90 per unit would still be extremely expensive. The most effective means to treatment cost reduction is through dosage reduction.

Genzyme's 1992 estimate of $2.74 includes business costs such as income taxes paid back to the Federal government and on-going research and development costs for the second-generation, recombinant product.

2. Second-generation Product

The recombinant product must be developed due to the limited supply of human placental tissue and to eliminate possible viral contamination issues associated with the first-generation product. For reasons which Genzyme does not fully understand, the OTA chose to exclude the financial impact of the recombinant product in their calculations of unit price and research and development costs.

While Genzyme continues to work with the NIH on the clinical trials for our recombinant product, we can proudly report that Genzyme is the sole developer. We expect to file an NDA within the next six months.

3. Genzyme's Investment for Treatments for Gaucher's Disease Exceeds $200M

Genzyme's investment to date in the development of treatments for Gaucher disease exceeds $200 million.

4. Ceredase® Costs are Declining through Dosage Reduction

The OTA report does not take into account the actual experiences of dosage reduction. The cost of Ceredase® treatment is rapidly declining toward our projected long-term therapy goal of between $20,000 to $60,000 per year. During the first 18 months since April 1991 product introduction, the cost of therapy through dosage reduction has declined by 50%. Genzyme expects an additional 50% reduction during the following 12 months.

5. Genzyme Did Not Receive Unfair Advantage by Government Agencies

Genzyme was never provided an exclusive license by the NIH for the placental -derived Ceredase® (alglucerase therapy). In fact, the enzyme lacks the patent protection typically available to new pharmaceutical products. Although the Orphan Drug Act (ODA) currently protects Ceredase®, this legislation does not preclude competitors to explore enzyme replacement therapies from alternative sources.

6. Highly-Effective Treatments Such as Ceredase® are Part of the Solution, Not the Problem

Health care expenses must be controlled. However, identification of appropriate cuts is difficult. We must challenge the effectiveness and the efficiency of our expenditures. A drug such as Ceredase® allows Gaucher patients to lead more normal, productive lives. In contrast, according to the OTA, patients with cystic fibrosis may incur direct medical expenses averaging more than $46,000 per year. But, patients die before age 30, despite the expenses.

We believe that the benefits of technological innovation should be made available to everyone. It is more acceptable to have a solution for a disease than to pay the costs resulting from no treatment. Health care expenses should be managed by challenging the inefficiencies of our system, including the high cost of non-efficacious treatments.

James Love
Taxpayer Assets Project
12 Church Road
Ardmore, PA 19003
v. 215/658-0880
f. 215/649-4066

Donna L. LaVoie
Manager, Public Relations
Genzyme Corporation
One Kendall Square
Cambridge, MA 02139-1562

Dear Ms LaVoie:

I am writing to respond to your letter of March 22, 1993 to Ralph Nader concerning our joint testimony before the Special Senate Committee on the Aging on February 24, 1993, concerning Federally Funded Pharmaceutical Inventions. You claim that we make two errors concerning Ceredase®, a product marketed by Genzyme Corporation. Your letter illustrates the need for better standardization of financial reporting by pharmaceutical companies.

1. You claim that the following statement is inaccurate:

> "According to the Company figures provided to the OTA, the cost of producing, manufacturing and marketing costs for Ceredase® was $1.90 per unit in 1992."

You believe that a "correct" statement would be that Genzyme's 1992 costs would be $1.90 for "producing" Ceredase®, and that Genzyme's costs would be $2.74 per unit if business costs such as income taxes and on-going research and development costs for a second-generation recombinant product were included.

In fact, the $1.90 figure given by OTA was not for producing Ceredase®, but rather, as we said, for producing, manufacturing and marketing. OTA does not break out the production and marketing costs separately. We never estimated the Genzyme income tax liability for its profits from Ceredase®, nor was it appropriate given our illustration of the mark-up from cost.

As for the cost of "on-going research and development" for a second-generation recombinant product, we do not believe that this is relevant to the cost of the current product Ceredase®, particularly since the new "second-generation" product, when and if it is developed, will likely be considered a patentable technology, unlike Ceredase®, which is protected under the Orphan Drug Act.

The issue of R&D investments in "second-generation" products was raised at length in our testimony in the context of Taxol. Bristol-Myers Squibb claims that the R&D costs associated with the development of "second-generation" Taxol® products should be used to justify its costs for Taxol®, a technology discovered and developed by the National Cancer Institution (NCI). We reject such arguments on the basis that consumers of the existing drugs should not be required to subsidize the company's investments in "second-generation" products, particularly when the companys will own the intellectual property rights to the new technologies.

The cross-subsidy issue is an important one. If companies which market government developed drugs justify large profits on the basis of research on new products, consumers of the existing drugs become involuntary investors in the new technologies. But unlike other investors, consumers will not earn any returns from their investments. If and when Genzyme markets such "second-generation" products, will it price the new products low, to reflect the fact that the consumers of Ceredase® have already paid for the R&D on the new product?

There is also an important anti-competitive effect. Since Genzyme Corporation's competitors do not have the benefits of such cross-subsidies, they must finance their R&D investments through competitive capital markets. Cross-subsidies from government developed drugs are not consistent with a level playing field.

2. You claim that it was inaccurate for us to say that in 1992 the $1.60 per unit "mark-up" over the $1.90 per unit cost for Ceredase® was 84 percent, and that a "correct" statement would be that a $1.90 unit cost and a $3.50 unit price represents a 46 percent "margin."

Your complaint on this matter is based upon our choice of the "mark-up over cost" rather than the "margin compared to price" to illustrate the profits on Ceredase®. Of course, both the 84 percent and the 46 percent figures are correct. The price is an 84 percent "mark-up over cost," and the "margin" is 46 percent of the price. It is not inaccurate to present the mark-up over cost figure, although the margin compared to price calculation is also a reasonable method of illustrating the profits.

1992 cost	=	1.90
price	=	3.50
1992 margin	=	1.60
1992 Mark-up over cost	=	margin / cost = 1.60/1.90
	=	84 percent
1992 Margin compared to Price	=	margin / price = 1.60/3.50
	=	46 percent.

Is their a single "correct" way to measure unit profits on drugs? No. There are several "correct" ways. Your cavalier use of the world "inaccurate" is at best misleading.

Sincerely,

James Love

cc: Ralph Nader
Senator David Pryor
John M. Coster

THE SCRIPPS RESEARCH INSTITUTE
10666 NORTH TORREY PINES ROAD
LA JOLLA, CALIFORNIA 92037
619 455-9100

February 24, 1993

The Honorable David Pryor
United States Senate
Washington, D.C. 20510

Dear Senator Pryor:

Today, at a hearing before the Senate Select Committee on Aging, Congressman Ron Wyden (D-OR) testified that The Scripps Research Institute (TSRI) had refused to provide to the National Institutes of Health (NIH) a copy of a private research funding agreement between TSRI and Sandoz Pharmaceuticals Corporation. That statement is completely inaccurate.

The facts are: On February 9, 1993, Dr. Bernadine Healy wrote a letter to TSRI requesting a copy of the agreement at issue. Three days later, representatives of TSRI met with officials of the NIH to address issues raised by the request, and to develop a mutually satisfactory means for responding. A number of complex issues were discussed, including the NIH's current unwillingness to assure that confidential, proprietary information contained in the agreement would be protected from public disclosure. Nonetheless, at the conclusion of that meeting, TSRI agreed to give further consideration to the agency's request, and to provide a written response within a reasonable time. At this point, the matter is still under consideration. TSRI expects to provide a written response within a week.

In addition, Mr. Wyden and others have implied that the funding agreement between TSRI and Sandoz is, in some unspecified respect, improper or perhaps contrary to federal law. This is a serious allegation for which there is absolutely no supporting evidence. Having been a recipient of federal grant support for more than 30 years, TSRI is fully aware of the terms and conditions governing the receipt of federal grants. TSRI intends to honor all of its obligations to the federal government, and has taken great care, in the context of its agreement with Sandoz as well as in all of its other activities, to assure compliance with all applicable federal requirements. Suggestions to the contrary are unfounded and unfair.

In order to correct misstatements made at today's hearing, TSRI respectfully requests that this letter be included in the official hearing record.

Sincerely,

William H. Beers, Ph.D.
Senior Vice President

C:\GENERAL\CORRES\022493.001

Bristol-Myers Squibb Company
655 15th Street, N.W., Suite 410 Washington, DC 20005 202 783-0900

Richard L. Thompson
Vice President
Government Affairs

March 2, 1993

The Honorable David Pryor
Chairman
Special Committee on Aging
U.S. Senate
SD-G31 Dirksen Senate Building
Washington, D.C. 20510-6400

Dear Senator Pryor:

I am writing on behalf of Bristol-Myers Squibb Company regarding your recent hearing on the government's investment in new drug development and appropriate pricing policies for drugs developed with government support. We are concerned about these important policy issues because their resolution will have far-reaching consequences for the National Institutes of Health, pharmaceutical manufacturers, research institutions, and the millions of patients who benefit from collaborative efforts among these parties.

Although Bristol-Myers Squibb did not testify at the hearing, we understand that several of our products were discussed by various witnesses. Unfortunately, it appears that inaccurate or misleading statements may have been entered into the record, particularly with regard to Taxol® (paclitaxel). Taxol® is an anticancer drug that was developed by Bristol-Myers Squibb pursuant to a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute and recently approved by the Food & Drug Administration for refractory ovarian cancer. We would like to correct these misstatements so that you are able to meet your stated goal of relying upon valid information as your Committee addresses these critical questions.

1. Several witnesses suggested that the reasonable pricing clause was unenforceable.

Bristol-Myers Squibb has a unique perspective regarding a private sector partner's duties under the reasonable price clause since the Company has developed the only two drugs, Videx® (dideoxyinosine) and Taxol® -- currently marketed pursuant to such language. Although the precise wording of the pricing clauses in the Videx® and Taxol® agreements varies to reflect the differences in the compounds' patent status (Videx® is patented and Taxol® is not), both address the government's concern that there be a reasonable relationship between the price of the marketed products and the public's investment in these products. I can state unequivocally that at no time did Bristol-Myers Squibb interpret either the statements or the Company's resulting contractual responsibilities to be unenforceable.

Instead, Bristol-Myers Squibb understood the reasonable price clause to impose real obligations regarding the pricing of both Videx® and Taxol® and it acted accordingly in its pricing decisions. Each of these drugs was priced in consultation with government officials, and each is priced within the range of comparable therapies. For example, Videx® was priced dramatically lower than the launch price of the only other antiviral drug available at the time of its introduction. Additionally, despite a huge investment, high production costs, and a limited period of exclusivity, the projected cost per cycle of Taxol® therapy is in the mid-range of other agents currently used in the treatment of refractory ovarian cancer.

In establishing fair and responsible pricing structures for Videx® and Taxol®, Bristol-Myers Squibb provided for a wide range of discounts to various groups and organizations, including a substantial and ongoing supply of free drug to the National Cancer Institute. Moreover, the Company has taken steps to ensure that no patient is denied access to these therapies because of an inability to pay -- reimbursement assistance and indigent patient programs are available for both Videx® and Taxol®. These measures demonstrate that Bristol-Myers Squibb took its responsibilities under the reasonable price clauses seriously, as did the government representatives with whom the Company dealt on the issue.

2. **Various witnesses apparently misunderstood Bristol-Myers Squibb's role in Taxol® development. For example, Rep. Wyden stated that according to a letter written by the Director of the National Cancer Institute, the government was totally responsible for discovering and developing Taxol®. Rep. Wyden went on to question what contributions, other than "put[ting] Taxol® in a pretty little box," Bristol-Myers Squibb had made to the project. In another instance, Mr. Nader described Bristol-Myers Squibb's role in developing Taxol® in the following manner: "BMS's only contribution to the NDA approval for Taxol® was to supply NCI with approximately 17 kilos of Taxol, and to process the paperwork for the NDA."**

Although Rep. Wyden failed to identify for the record the precise letter to which he referred, in a previous hearing he based a similar characterization of the Taxol® project on a letter written by Dr. Samuel Broder on September 10, 1991, less than eight months after the Taxol® CRADA was signed (see Tab A for pertinent portions of the agency's 9/10/91 response). Although this letter lists a number of activities which the National Cancer Institute had undertaken with regard to Taxol®, this recitation must be read with the knowledge that Bristol-Myers Squibb was in the process of dramatically expanding its activities so as to meet its commitments under the CRADA. Even Dr. Broder acknowledges this important fact, as his full statement reads "[T]herefore, **until the transfer of certain responsibilities to Bristol-Myers Squibb under the CRADA**, NCI was totally responsible for its development." Letter from Samuel Broder, M.D., Director, National Cancer Institute, to Rep. Ron Wyden, Chairman, Subcommittee on Regulation, Business Opportunities and Monopolies of the House Committee on Small Business (Sept. 10, 1991).

We fear that Rep. Wyden's mischaracterization of Dr. Broder's statement may mislead individuals who are not familiar with the Taxol® project. Since the CRADA was signed in January, 1991, the Company has made Taxol® its number one research priority. In only two years, we have invested several times the $32 million spent on Taxol® by the National Cancer Institute -- and far in excess of the CRADA figure of $114 million. In addition, Bristol-Myers Squibb personnel have devoted more than 205 staff years to making Taxol® widely available to patients -- again far in excess of the CRADA figure of 125 staff years. These figures, which reflect the Company's expenditures as of the date of Taxol® approval, do not include any costs for advertising, marketing or promoting Taxol®.

Among the major activities which Bristol-Myers Squibb undertook to meet its CRADA obligations were the following: 1) collect and analyze clinical data; 2) supply the National Cancer Institute with Taxol® at no charge to support clinical trials and compassionate use protocols; 3) secure adequate quantities of Pacific yew, currently the only approved source of Taxol®; 4)

institute procedures to comply with good manufacturing practices guidelines; 5) scale-up manufacturing processes to produce large quantities of Taxol®; 6) resolve formulation issues; 7) prepare and file a New Drug Application; 8) implement a distribution system to make Taxol® widely available to patients upon its approval; and 9) undertake an aggressive search for, and development of, alternative sources of Taxol®.

The activities described above represent only a partial summary of some of the most significant steps which the Company had to take in order to make Taxol® widely available to cancer patients. However, a complete understanding of the unique challenges overcome by Bristol-Myers Squibb is not possible unless one is fully aware of the historic sourcing difficulties associated with producing Taxol®. At the time the CRADA was signed, the National Cancer Institute was producing only one kilogram of Taxol® every two years. Through its aggressive sourcing strategy, Bristol-Myers Squibb has been able to ensure that enough Taxol® will be available to treat patients for whom the drug is appropriate and to supply the National Cancer Institute with Taxol® to support clinical trials and compassionate use programs. In addition, the Company's successful search for alternative sources of Taxol® has resulted in a semi-synthetic process which we anticipate will produce significant amounts of Taxol® by the end of 1993.

Thus, it is simply not accurate to minimize Bristol-Myers Squibb's contributions to this significant and highly successful collaborative endeavor by describing its efforts as merely packaging Taxol® into "pretty little boxes," or supplying 17 kilos of drug to the National Cancer Institute and preparing an NDA. Upon signing the CRADA, Bristol-Myers Squibb immediately made Taxol® its top research and development priority, a decision which required an extremely large and ongoing investment of both dollars and personnel, and which blocked the Company's pursuit of other promising projects in our research pipeline. As a direct result of this investment, Taxol® is now available to any patient in the U.S. who might benefit from it.

3. **Some witnesses inaccurately described the cost of Taxol® therapy. For example, the Committee's staff report asserts that Taxol® will cost $9,350 for full eight cycle treatments. Mr. Nader's statement maintains that "[T]he cost of a completed Taxol treatment will exceed $10,000 for some patients."**

Neither of these figures accurately reflects the average cost of Taxol® treatment for refractory ovarian cancer patients.

The figures quoted above apparently were derived without considering either the many patients who will benefit from the numerous discounts and rebates available to a variety of purchasers or those patients who will receive the drug without charge through the Taxol® Access Program. More importantly, these estimates are based on patients receiving at least eight cycles of Taxol®, a number that simply is not typical for patients being treated with Taxol® for ovarian cancer.

In assessing the cost of Taxol® treatment, it is most accurate to examine the projected cost per cycle of therapy. In treating ovarian cancer patients, Taxol® is administered in cycles, each of which consists of a recommended dose of 135mg/m2 given intravenously by continuous infusion over 24 hours every three weeks. The National Cancer Institute has described typical Taxol® therapy for ovarian cancer in the following manner: "For refractory ovarian cancer, patients receive treatment until they show signs of progressive disease. Thus, approximately 50 percent will receive 2-3 cycles of treatment while the remaining 50 percent, who have stable disease or respond to treatment, will be treated for an average 5-6 cycles of therapy." Obviously, dosages and treatment schedules vary according to the treatment plan for each individual.

Taking into account the range of prices associated with different methods of distribution, the net effective weighted average cost of Taxol® per cycle is $695.25. At the wholesale list price, which is the highest price Bristol-Myers Squibb will charge for Taxol®, the projected cost per cycle of therapy is $986.18. These figures are well below those of many other recently approved cancer therapy agents and in the mid-range of other agents currently used in the treatment of ovarian cancer.

Thus, an "average" regimen consisting of four cycles of Taxol® therapy at a net effective rate of $695.25 per cycle would result in a total cost per patient of less than $3,000. Even an intensive regimen consisting of six cycles of Taxol® therapy at the wholesale (highest) price of $986.18 would amount to a total cost per patient of less than $6,000. Both figures are far below the sums cited by the Committee's report and Mr. Nader.

4. **Mr. Nader alleges that "a child with a fourth grade education and a pencil and paper could have easily estimated BMS's development and manufacturing costs from a review of publicly available SEC documents." He apparently bases this statement on a filing by Hauser Chemical with the Securities and Exchange Commission in which he deduces that Hauser will be paid $100 million to produce 400 kilograms of Taxol® for BMS through 1994.**

Bristol-Myers Squibb regards production cost information to be confidential and proprietary, so a detailed response is not possible. However, we believe that this statement demonstrates a complete misunderstanding of the drug development process and its various requisite parts. Bristol-Myers Squibb's payments to Hauser Chemical, which manufactures only bulk paclitaxel under contract to the Company, are not representative of the costs which Bristol-Myers Squibb incurs in making Taxol® available to patients. As outlined in the answer to Question 2, many other activities are necessary steps in the drug development and manufacturing process. It is extremely misleading to suggest that accurate development and manufacturing costs can be extrapolated from limited, and very general, information provided by one of the Company's contractors.

5. **Mr. Nader's statement points out that 11 of the 34 cancer drugs developed with government funding since the initiation of the National Cancer Institute's new drug program are marketed by Bristol-Myers Squibb. He concludes his statement by declaring that "[M]embers of Congress need to examine the NCI/BMS relationship to better understand why this company has received so much from our government."**

In 1971, Congress recognized in the National Cancer Act the need for a focused approach to cancer research and oncologic drug development. This Act directs the National Cancer Institute to coordinate an expanded and intensified cancer research program in order to efficiently allocate scarce research dollars. As a result of this statutory mandate, the National Cancer Institute has assumed a leading role in the conduct of basic and clinical cancer research in this country; consequentially, the Institute

has contributed, in varying degrees, to the research and development of nearly all of the cancer drugs that have been approved in the last twenty years. The agency participates in all phases of drug development, as it operates a large-scale screening program to identify promising agents, conducts initial pre-clinical work to determine the potential activity of these compounds, and designs clinical trials to assess the safety and efficacy of promising anticancer drugs. In fact, many of the clinical trials performed in the U.S. are run through the Institute's designated Cancer Centers and a network of nationally recognized clinical investigators.

The pivotal role which Congress envisioned for the National Cancer Institute was necessitated by a growing sense that only a concerted effort emphasizing collaborations between the government and private industry would suffice to meet the growing public health threat posed by cancer. Both the intricacies of drug development in general and the particular challenges associated with understanding cancer and identifying potential therapies which might successfully prevent, cure or arrest this disease supported the Congressional decision to encourage such a coordinated approach.

In the article from which Mr. Nader derived much of his list of 34 drugs, Dr. Chabner and Dr. Shoemaker of the National Cancer Institute also stress the need for increased cooperation between government, industry, and academia if progress against cancer is to occur. During the hearing, Dr. Chabner alluded to the difficulties involved in developing oncology products when he noted that only those companies possessing the requisite scientific and regulatory foundation are capable of bringing anticancer drugs to the market quickly. He acknowledged that development of the therapies which the National Cancer Institute has supported has not always proceeded smoothly because the agency's private sector partners simply lacked the capability to take a product through this demanding process or have failed to work closely with the National Cancer Institute.

Bristol-Myers Squibb, on the other hand, has been committed to the development of oncology products for more than thirty years, and is widely recognized as the leader in the field. We value this position and feel an obligation to develop and provide the best possible new therapies to the oncology community. Because of our dedication to this therapeutic area, Bristol-Myers Squibb has the personnel, resources, expertise, and infrastructure in place to make oncology drugs widely available in the most expeditious manner possible to the patients who may benefit from them.

Bristol-Myers Squibb believes that Congress was correct when it decided that the best way to meet these important goals is through a comprehensive national strategy whereby the National Cancer Institute collaborates with leading cancer experts at research institutions and qualified pharmaceutical companies to quickly identify and develop promising anticancer therapeutics. Consistent with this belief, our Company has made a concerted effort to work with the agency designated by Congress to spearhead this nation's fight against cancer. We have supported, and will continue to support, the Institute's efforts to ensure that designated developmental priorities and clinical research programs address the most important needs and opportunities presented by each potential anticancer drug. Indeed, it is because of this collaborative effort that a number of important new agents for the treatment of cancer have been made available in a relatively short period of time.

Thus, it is the respective roles and strengths of the National Cancer Institute and Bristol-Myers Squibb, as envisioned by Congress in the National Cancer Act, which explain the close, collaborative relationship between these two parties in making anticancer therapies accessible to patients.

Thank you for allowing Bristol-Myers Squibb to submit these clarifications for the record.

Sincerely,

Richard L. Thompson

TAB A

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

September 10, 1991

The Honorable Ron Wyden
Chairman
Subcommittee on Regulation,
Business Opportunities and Energy
B-363 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Wyden:

It is our pleasure to respond to your request for additional information on the National Cancer Institute's (NCI) efforts with regard to the development of Taxol and the CRADA process. Although I was personally unable to testify at your hearing, I wish to thank you for giving Dr. Bruce Chabner, Director, Division of Cancer Treatment, NCI an opportunity to articulate NCI's commitment to drug development.

As you requested, enclosed is a folder of NCI's response to the questions you posed in your August 1, 1991 letter along with some additional background material. I hope this information addresses your concerns satisfactorily.

Perhaps we could take this opportunity to thank you for providing us an opportunity to clarify a number of issues that, in fact, could not have been presented in any other forum. We want you to know how important your support and the support of the other subcommittee members is to the success of the National Cancer Program

Sincerely yours,

Samuel Broder, M.D.
Director
National Cancer Institute

Enclosure

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* NCI'S Response to Questions Raised in Representative Ron Wyden letter dated August 1, 1991.

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* TABS (A-G)

A. "Request for Exclusive License Extension," 48 Federal Register 5313 (February 4, 1983) -- Supports Response 5a.

B. "Decision to Extend Exclusive License," 48 Federal Register 53,177 (November 25, 1983) -- Supports Responses 5b-d.

C. "Intent to Grant Exclusive Patent License; Bristol-Myers," 52 Federal Register 41612 (October 29, 1987) -- Supports Response 7a.

D. Memorandum dated July 24, 1987 from Dr. Vincent DeVita to Dr. Robert E. Windom concerning the Selection of Awardee for Exclusive License to ddI and Dr. Windom's response -- Supports Response 7n.

E. "Request for Establishment of Collaborative Agreement for the Preclinical and Clinical Development of Dideoxyadenosine/Dideoxyinosine as an Anti-Viral Agent Useful in the Treatment of Acquired Immunodeficiency Syndrome (AIDS)," Federal Register (May 8, 1987) -- Supports Response 7n.

F. Azidothymidine (AZT) Chronology -- Supports Response 8a.

G. "Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Scientific and Commercial Development of Taxol as an Anticancer Agent," 54 Federal Register 31733 (August 1, 1989) -- Supports Response 10C.

Question 9. All witnesses at the hearing acknowledged the important role of NCI in developing Taxol.

Answers (9a-d):

a. Please describe the government's role in the development of Taxol?

Taxol was discovered and developed within the NCI's comprehensive anticancer drug development program. Therefore, until the transfer of certain responsibilities to Bristol-Myers Squibb under the CRADA, NCI was totally responsible for its development. This responsibility, effected primarily through contracts, included (1) the initial collection and recollection of bark; (2) all biological screening in both cell culture and animal tumor systems; (3) chemical purification, isolation and structure identification; (4) large-scale production, from collection of bark through preparation of material suitable for human use; (5) development and production of a suitable intravenous dosage formulation; (6) preclinical toxicology; (7) filing of an Investigational New Drug Application (INDA) with the FDA, along with all required documentation; and (8) sponsorship of all clinical studies. In addition, a broad array of research activities, including efforts directed toward total and partial synthesis of the drug, have been supported through NCI research grants and intramural programs.

b. How much money has the government spent, each year, on Taxol research, tests, and clinical trials?

It is impossible to obtain precise cost information for the period prior to 1977. We estimate that these costs, including collection, screening, and chemical purification activities, totalled about $234,000. Costs since that time are summarized below, although it should be pointed out that they are also estimates, since they represent in most cases portions of larger contracts or grants.

YEAR	DOLLARS (thousands)	YEAR	DOLLARS (thousands)
1977	36	1984	851
1978	73	1985	760
1979	114	1986	1,140
1980	140	1987	1,568
1981	477	1988	1,483
1982	250	1989	1,501
1983	446	1990	2,150

c. What patents exist for Taxol, Taxol analogues, Taxol processes, or other related Taxol matters does NCI hold? How many of these patents have been licensed?

There are no patents on Taxol itself. The first laboratory results with taxol were published in the 1970's by researchers who did not obtain patents. There is one application pending, relating to a Taxol pro-drug, a compound derived from Taxol which is more soluble than Taxol and which would be converted to Taxol after administration. This invention, in which the government is a co-owner, has not yet been licensed.

d. Please describe NCI's plans for future Taxol research, testing, and clinical trials. What are the estimated budgets for these endeavors?

NCI will continue to support vigorous laboratory research on Taxol through its research grants mechanisms. These investigator-initiated studies range from basic biochemical and pharmacological studies to efforts directed toward total synthesis, and are likely to continue covering a wide variety of areas. This research is currently being supported at a level of about $2.6 million annually and is likely to increase because of the intense interest in this highly important drug.

NCI will also continue to support clinical trials with Taxol. For an active agent such as Taxol, Phase II testing is typically carried out in approximately 30 different types of cancer. Phase II testing has been completed or is near completion in six (6) malignancies, leaving 24 to be initiated and completed. The cost of these additional trials is estimated to be about $3 million. In addition, Phase III trials would be conducted in malignancies that are sensitive to Taxol. At present, those include breast and ovary, but we anticipate that perhaps another 10 malignancies will be sensitive to Taxol and require large-scale Phase III trials. The cost of these trials, carried out over a period of several years, is estimated to be about $20 million. Therefore, the total future cost of clinical trials is estimated to be approximately $23 million.

The NCI plan to determine the range of activity and specific indications for taxol is typical of our participation in the development of most of the known active anti-cancer agents, whether they are NCI-patented or company-owned products. NCI interprets its primary mission to be the development of cures for cancer, or failing that, the development of agents to prolong survival and alleviate suffering. A decision to develop a new drug would depend strictly on these criteria, and not upon what organization owned the patent.

March 17, 1993

The Honorable David Pryor
United States Senate
Chairman, Special Committee on Aging
267 Senate Russell Office Building
Washington, D.C. 20510

Dear Mr. Chairman:

At the end of your hearing on the federal government's investment in new drug research and development, Mr. Gerald J. Mossinghoff, President of Pharmaceutical Manufacturers Association, made several comments concerning current litigation between Barr Laboratories and Burroughs-Wellcome, which may have left the Committee with an incorrect perception of the status of the suit. I would like to correct the record.

Barr Laboratories is a manufacturer of generic drugs headquartered in Pomona, New York. In early 1991 representatives of Barr approached the National Institutes of Health (NIH) to inquire about the government's claim to patent rights to the AIDS drug, AZT. As a result of these discussions, on July 11, 1991, Barr Laboratories received a non-exclusive license from NIH to manufacture and market a generic AZT. Barr will pay NIH a royalty for all AZT manufactured under the authority of this license.

The agreement obligates the company to pursue the NIH patent claim in federal court at its own expense. These legal costs exceed $2 million to date and will cost at least an additional $1.5 million to take the case to trial. The trial is currently scheduled for June of this year. Under the Waxman-Hatch Act, should Barr be successful in establishing that NIH scientists are co-inventors of AZT, the company would be entitled to six months of market exclusivity after which time any other generic drug firm would be able to market a version of AZT subject to FDA approval and license from NIH.

During the negotiations leading to the agreement with NIH, Barr offered to specify a price it would charge for AZT during the period of exclusivity in the contract. NIH declined the offer. Nonetheless, Barr has promised that it will sell the drug at approximately 50% of the Burroughs price unless that price failed to cover Barr's costs.

Barr's entry into the market would dramatically reduce the price of AZT for persons infected with the HIV virus. Similarly, it would substantially reduce the price for AZT paid by the federal government, which has already spent through direct and indirect payments roughly $500 million on AZT.

At the hearing, Mr. Mossinghoff inaccurately implied that the validity of Burroughs-Wellcome patent was being disputed only by Barr Laboratories. He stated that NIH had asked to be dismissed from the suit and had been. Mr. Mossinghoff is simply wrong.

Technically, NIH has never been a party to the litigation between Burroughs-Wellcome and Barr Laboratories. In accordance with the agreement with NIH and current patent law, Barr Laboratories notified Burroughs-Wellcome of its intent to manufacture a generic version of AZT under a licensing agreement with NIH. Thereafter, Burroughs-Wellcome filed suit against Barr in U.S. District Court for the Eastern District of North Carolina, where Burroughs-Wellcome is located.

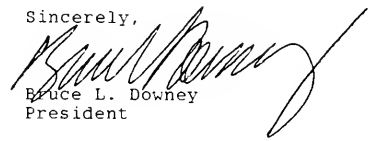
NIH was never a named party to this suit: consequently, it was not dismissed from the case. In fact, agency officials have been cooperative and have worked with Barr's attorneys as they prepare for trial. In a very real sense, Barr Laboratories is representing the interests of the NIH and the federal government in this litigation. Unfortunately, the Department of Justice has yet to formally intervene in the suit on behalf of NIH. The new Attorney General, Janet Reno, has the issue under review.

In a separate action, on March 18, 1991, Public Citizen filed a suit against Burroughs-Wellcome on behalf of an AIDS health group and two patients, attempting to invalidate the AZT patent. The suit named the United States government as a defendant in order to force the federal government to take a position on its ownership interests in the patent. Shortly after the suit was filed, NIH Director Bernadine Healy issued a statement confirming that the National Cancer Institute scientists deserved to have their names listed as inventors on the patent. The Justice Department, as a matter of routine procedure when the government is named as a defendant in a law suit, did ask for dismissal from the suit filed by Public Citizen. However, NIH entered into the license agreement with Barr Laboratories.

Barr Laboratories hopes that the Clinton Administration, with its commitment to control the spiraling cost of drugs and to help the victims of this terrible plague, will view the importance of this lawsuit differently than the previous administration. Trying a case involving a firm as large as Burroughs-Wellcome in its own backyard is extremely difficult. Given the overriding public interest, the fiscal consequences to the taxpayers that financed the research, and the simple justice owed to the courageous researchers at NIH, one would expect that the Department of Justice would be enthusiastic about supporting Barr's efforts in court. Naturally, its intervention would be welcome.

As you noted in your opening statement, it is hardly a fair deal for Americans to subsidize the development of medications like AZT and then be forced to pay high prices for drugs they already helped to bring to market. Barr Laboratories is committed to reducing the price of AZT by introducing a generic version of the drug, which we believe will help to rectify the serious problems you identified at your hearing. Thank you for giving us an opportunity to correct the record.

Sincerely,



Bruce L. Downey
President

cc: Senator William Cohen

ISBN 0-16-040848-2